UNIVERSITY OF
ILLINOIS LIBRARY
AT URBANA-CHAMPAIGN
[redacted]

Digitized by the Internet Archive
in 2012 with funding from
University of Illinois Urbana-Champaign

http://archive.org/details/organicsemi1973751univ

3/0

ORGANIC SEMINAR ABSTRACTS

1973-74

Semester I

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois

THE LIBRARY OF THE
[illegible] 1974
UNIVERSITY OF ILLINOIS

SEMINAR TOPICS

I Semester 1973-74

Arsonium Ylides in Organic Synthesis....................1
David Wiemer

The Mechanism of Head-to-Head Terpene Biosynthesis....................10
David Ley

Recent Studies on Asymmetric Reductions....................12
Richard W. Thomas

New Annelation Methods and their Applications in Organic Synthesis....................21
Alex M. Nadzan

Oxaspiropentanes: Formation and Use as Synthetic Intermediates....................30
Richard L. Neeley

Rationale for the Gauche Effect....................39
Tyler Thompson

Tetracyanoquinodimethane (TCNQ) and its Molecular Complexes....................41
Gautam Desiraju

Affinity Chromatography....................50
Hansen M. Hsiung

Recent Applications of Alkali Metal N,N-Dialkylamides....................59
George Luteri

Recent Developments in the Chemistry of Benzene Valence Bond Isomers....................61
Gaylen R. Brubaker

Some Recent Studies of Organic Chemiluminescent Systems....................68
E. Robert Fretz

Controversial Stereochemical Interpretations of Nucleophilic Additions ($H^{\ominus}$ and $R^{\ominus}$) to Ketones....................77
May D. Lu

Recent Uses of the Iron Carbonyls in Organic Chemistry....................86
Arthur Haber

Synthesis and Properties of Heterocycles Containing Tetravalent Sulfur Atoms....................95
Kenneth Christy

Carbanion Rearrangements: 1,2 Shifts and ω-Olefin Cyclizations....................97
Patricia L. Cavender

Photoaddition Reactions of Benzene to Olefins....................106
William F. Pfohl

ARSONIUM YLIDES IN ORGANIC SYNTHESIS

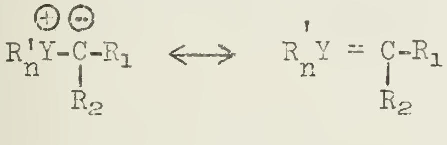
Reported by David Wiemer September 10, 1973

SCOPE

Although the first arsonium ylide was apparently synthesized in 1902 by Michaelis,[1] this class of ylides has been little studied until the past few years. Arsonium ylides have been included in reviews of organometallic chemistry[2,3] and they were included in a general review of ylide chemistry in 1966,[4] but at that time they had no recognized synthetic utility. This seminar will cover material since the general review, especially the synthesis of arsonium ylides and their possible synthetic applications.

INTRODUCTION

An ylide is defined as a compound in which two adjacent atoms bear opposite formal charge, but the negative atom, usually carbon, cannot donate its unshared pair because the positive atom has a filled octet. If the positively charged atom can easily expand its valence shell, the resonance hybrid will have more covalent character and will more closely resemble 2.



$$R'_n\overset{\oplus}{Y}-\overset{\ominus}{\underset{R_2}{C}}-R_1 \longleftrightarrow R'_nY=\underset{R_2}{C}-R_1$$

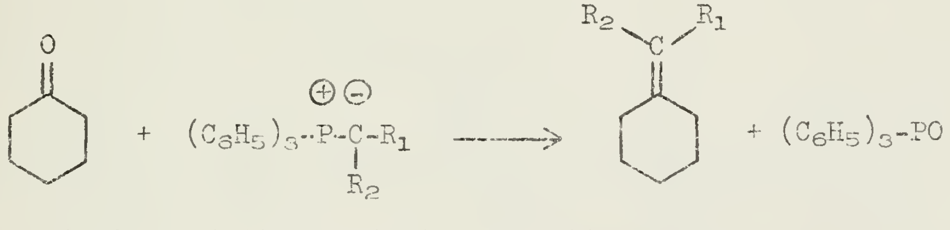
1 2

Y = P, As, Sb, Bi n = 3

Y = S, Se, Te n = 2

Ylides in which phosphorus is the positive atom are the best known,[4,5] although ylides involving sulfur and nitrogen are frequently used and ylides involving arsenic, selenium, tellurium, bismuth, antimony and others are known.[6] In principle, R' can be any alkyl or aromatic group and the R' groups need not be identical. In practice, triphenyl ylides are used almost exclusively since there is no question as to which carbon carries the negative charge.

The principal synthetic application of phosphonium ylides is the conversion of carbonyls to olefins in the Wittig reaction. In many instances, the Wittig synthesis offers significant advantages in generating olefins. It gives unambiguous location of the double bond, and it can be used to give non-conjugated olefins inaccessible by other routes. Examples of its use are the formation of olefins with exocyclic double bonds and the formation of β,γ-unsaturated acids and esters.

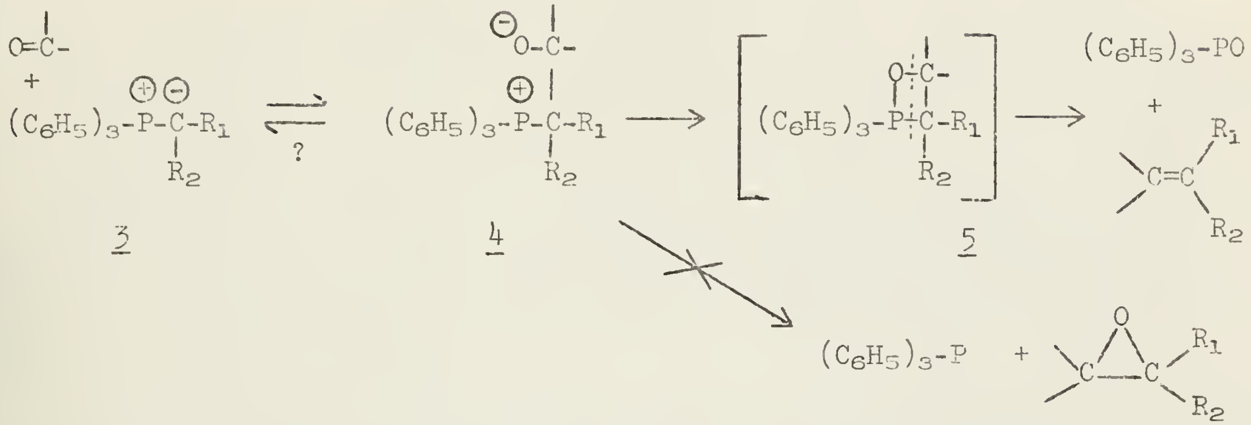


The principal limitation to this reaction is that if either R_1 or R_2 is electron withdrawing, the reaction is slow; if both are electron withdrawing, the ylide is stabilized sufficiently so that there is no reaction. Attempts to overcome this limitation have included the use of phosphonate-derived ylides[7] and trialkylphosphoranes[8] instead of triphenylphosphoranes. Recent attempts to overcome this limitation of the Wittig reaction have involved the use of arsonium ylides instead of phosphonium ylides.

Study of the mechanism of the Wittig reaction[4] reveals the basis of this limitation (Scheme 1). The phosphonium ylide 3 adds to the carbonyl compound to form the betaine intermediate 4, followed by elimination of triphenylphosphine oxide and generation of the olefin. If neither R_1 nor R_2 is electron withdrawing,

the slow step is the elimination of triphenylphosphine oxide. The strength of the phosphorus oxygen bond drives the reaction to the alkene. If R_1 and R_2 are

Scheme 1

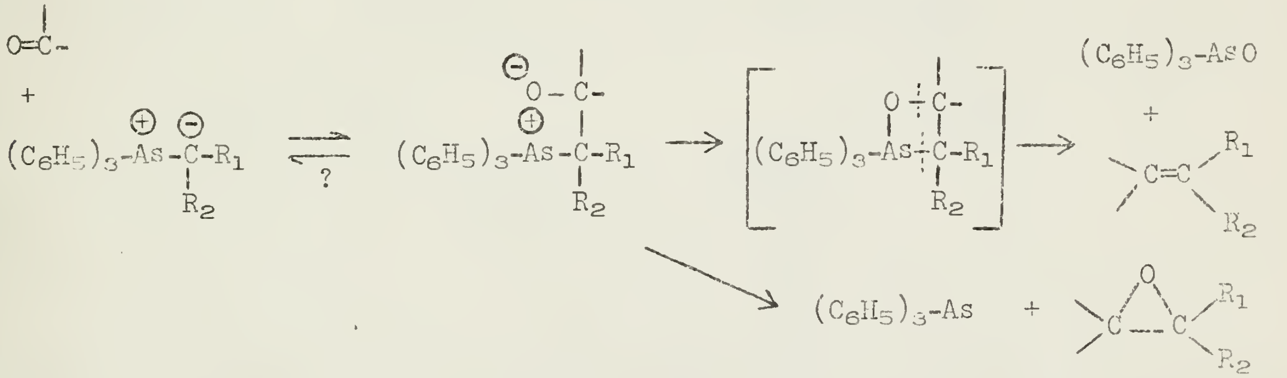


sufficiently electron withdrawing, the carbanion is stabilized and becomes non-reactive. Formation of betaine 4 is then rate limiting. Although the mechanism of the reaction between carbonyls and arsonium ylides has not been studied as extensively as that of phosphonium ylides, an analogous mechanism is generally accepted.[9]

There are two important differences in the properties of arsenic relative to phosphorus. First, studies of the basicity of arsonium ylides have shown that they are 200 to 230 times more basic than their phosphorus analogues.[10] This suggests that the dipolar form (1) has a significatly larger contribution with arsenic than with phosphorus. In addition, electric dipole moment studies indicate that arsonium ylides are more polar than phosphonium ylides. This is readily rationalized since the 4d orbitals of arsenic should be more diffuse than the 3d orbitals of phosphorus and give less overlap with the carbanion. This increased polarity should increase reactivity.

The second important difference between arsenic and phosphorus is the weakness of the arsenic-oxygen bond (93kcal/m) compared with the phosphorus oxygen bond (156 kcal/m). The greater strength of the P-O bond drives reactions exclusively to triphenylphosphine oxide and the alkene. With arsonium ylides, the formation of the As-O bond is not as strong a driving force; epoxides or their rearrangement products are sometimes obtained instead of olefins (Scheme 2).

Scheme 2



In general, olefins result from the Wittig reaction of arsonium ylides stabilized by electron withdrawing groups, while arsonium ylides without electron withdrawing groups give epoxides or mixtures of epoxides and olefins. There are two explanations for this. According to Lloyd[6] et al. and Johnson,[11] with stabilized arsonium ylides, the olefinic bond formed will be part of a conjugated system. Conjugation stabilizes the transition state leading to the alkene and an alkene is the exclusive reaction product. Trippet and Walker[12] propose that the carbon-arsenic bond begins breaking in advance of the other electron shifts, giving the

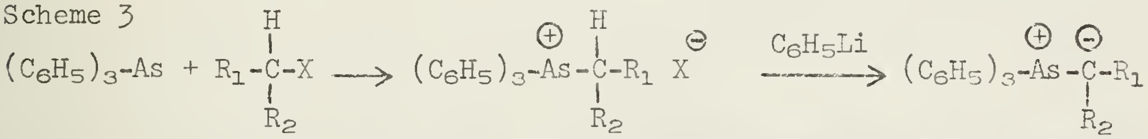
α-carbon a fractional negative charge. The transition state would be stabilized by electron withdrawing groups and the alkene would become the favored product. Although Trippet and Walker examined a series of arsonium ylides with and without electron withdrawing groups, their work does not rule out the earlier theory. The electron withdrawing substituents that they employed would also provide conjugative stabilization. It is unfortunate that they did not examine ylides in which the two effects could be separated. Product studies on arsonium ylides with electron withdrawing groups which cannot stabilize through conjugation should support one but not both of these hypotheses.

Since epoxide products can be prepared via sulfonium ylides, and alkyl substituted olefins can be prepared via phosphonium ylides, arsonium ylides will largely find application in the preparation of olefins where R_1 and R_2 are electron withdrawing groups. In such a case, if they react with carbonyls, alkenes are afforded cleanly.

PREPARATION OF ARSONIUM YLIDES

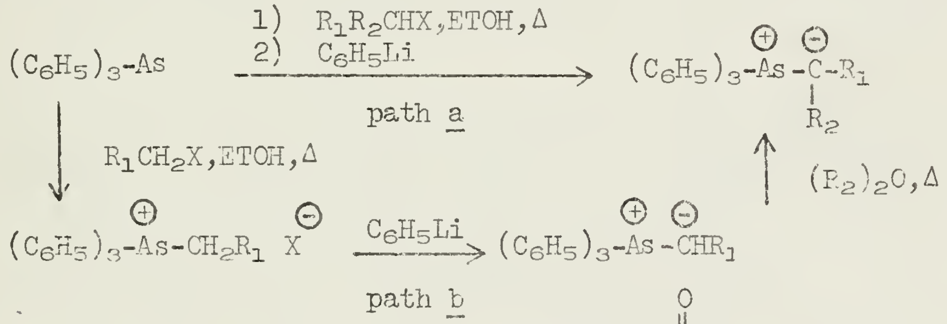
Most of the methods used to prepare arsonium ylides are analogous to those used to prepare phosphonium ylides. The oldest and most common method is the "salt" method.[1,13] Triphenylarsine is heated to reflux in ethanol with excess alkyl halide to give the triphenylalkylarsonium salt. The salt is then suspended in ether and treated with a molar equivalent of phenyl lithium to generate the ylide. If the ylide is stabilized by electron withdrawing groups, it can be

Scheme 3



$$(C_6H_5)_3\text{-As} + R_1\text{-}\underset{R_2}{\overset{H}{C}}\text{-X} \longrightarrow (C_6H_5)_3\text{-}\overset{\oplus}{As}\text{-}\underset{R_2}{\overset{H}{C}}\text{-}R_1\ \overset{\ominus}{X} \xrightarrow{C_6H_5Li} (C_6H_5)_3\text{-}\overset{\oplus}{As}\text{-}\underset{R_2}{\overset{\ominus}{C}}\text{-}R_1$$

isolated as a crystalline solid. If it is an "unstabilized" arsonium ylide, it must be used in solution. The salt method is not always satisfactory, particularly if there are two strongly electron withdrawing groups. Lloyd and Gosney[14] claimed that "nucleophilic removal of the halogen atom and formation of a carbanion..." interfered with formation of the arsonium salt, but they offer no evidence. Synthesis of a mono β-ketoylide by the salt method can serve as an alternate synthetic route. This reaction proceeds smoothly since there is only one electron withdrawing group. The ylide can then be acylated by heating it in a carboxylic anhydride.



if $R_1 = -\overset{O}{\overset{\|}{C}}-R$ R,R' = alkyl or aromatic

$R_2 = -\overset{O}{\overset{\|}{C}}-R'$

path b must be used

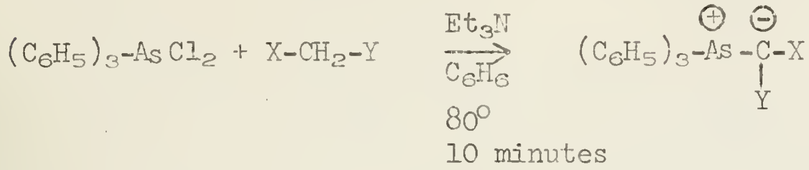
if R_1 or $R_2 = -\overset{O}{\overset{\|}{C}}-R$

and

R_1 or R_2 = alkyl or aromatic

path a is satisfactory

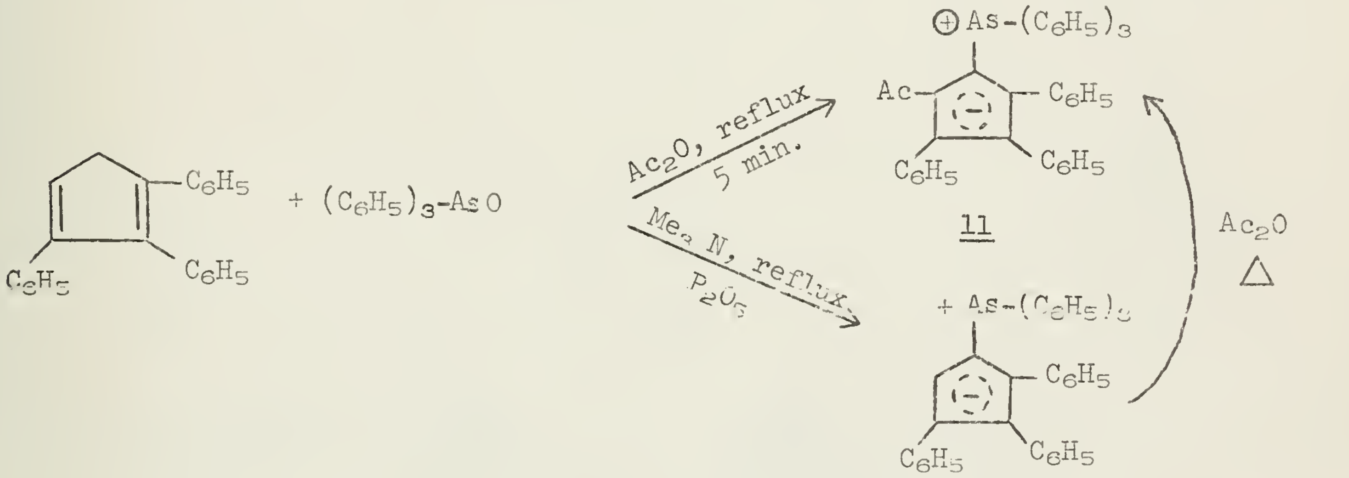
Triphenyl arsine dichloride will react with active methylene compounds to form ylides. Horner used this method[15] to synthesize ylides 6-9. Outside of his work, this method has found little application.



$$(C_6H_5)_3\text{-AsCl}_2 + X\text{-CH}_2\text{-Y} \xrightarrow[C_6H_6,\ 80^\circ,\ 10\text{ minutes}]{Et_3N} (C_6H_5)_3\text{-}\overset{\oplus}{\text{As}}\text{-}\underset{\text{Y}}{\overset{\ominus}{\text{C}}}\text{-X}$$

#	X	Y	Yield
6	$-CN$	$-CO_2Me$	62%
7	$-NO_2$	$-C_6H_5$	23%
8	$-CN$	$-CN$	54%
9	$-CO_2C_6H_5$	$-CO_2C_6H_5$	49%

Triphenylarsonium tetraphenylcyclopentadienylides have been prepared from triphenylarsine and diazotetraphenylcyclopentadiene by heating the mixture until it is molten.[16] The reaction presumably proceeds through a carbene intermediate.[17] However, yield was not reported and when the reaction was attempted with diazotriphenylcyclopentadiene, there was no detectable reaction.[18] As an alternative route to the phenylcyclopentadienylides, the condensation of triphenylarsine oxide with cyclopentadienes was attempted.[19] When a mixture of 2,3,4-triphenylcyclopentadiene and triphenylarsine oxide was heated to reflux in trimethylamine over phosphorus pentoxide, the ylide 10 was produced in 55% yield. When 2,3,4-triphenylcyclopentadiene was heated to reflux in acetic anhydride with triphenylarsine oxide, the ylide 11 was produced in 70% yield, presumably arising from acylation of ylide 10. As part of the structure proof, the ylide 10 was converted into the ylide 11 by heating it in acetic anhydride.



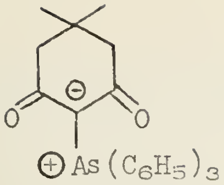
11

10

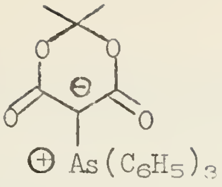
Recently the series of stabilized arsonium ylides 12-26 was prepared by Gosney and Lloyd[20] using both the condensation of carbon acids with triphenylarsine oxide and the carbene method (Table 1). In general, the arsine oxide/carbon acid/acetic anhydride method gives higher yields. Since compounds such as diethyl malonate, fluorene, acetophenone and phenylacetonitrile do not react, a fairly strong carbon acid appears to be necessary. There is also the danger of acylating the ylide originally formed.

Many of the ylides 12-27 were also synthesized by the carbene method. For the carbene reactions, a mixture of triphenylarsine and the diazo compound was heated under a nitrogen atmosphere until molten. Nitrogen was evolved vigorously and the products obtained are identical to those obtained through the carbon acid method. Copper, copper-bronze or copper salts were used as catalysts. No ylides were evolved from monoacyldiazo compounds such as ethyldiazoacetate or p-nitrobenzoyl diazomethane.

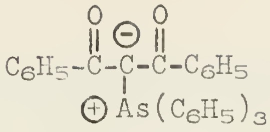
Interestingly, the unacylated ylide 26 can be obtained using triethylamine/phosphorus pentoxide. This ylide can be converted into the acetylide 18 by brief heating in acetic anhydride. Ylide 26 is thermally stable whereas the



12

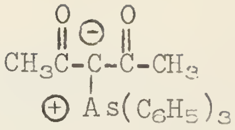


13



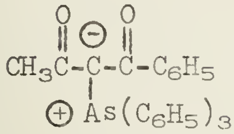
$C_6H_5-\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5$

14



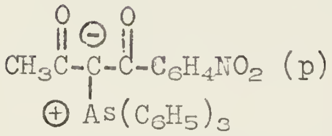
$CH_3\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-CH_3$

15



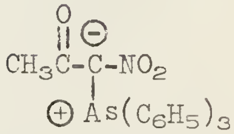
$CH_3\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5$

16



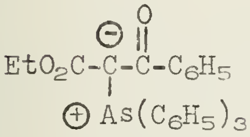
$CH_3\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_4NO_2$ (p)

17



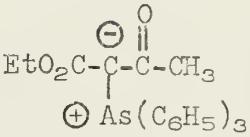
$CH_3\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-NO_2$

18



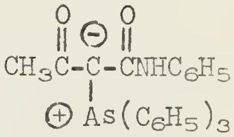
$EtO_2C-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5$

19



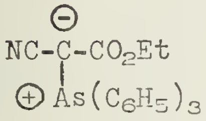
$EtO_2C-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-CH_3$

20



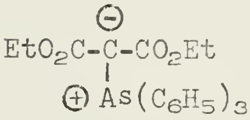
$CH_3\overset{O}{\overset{\|}{C}}-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}NHC_6H_5$

21



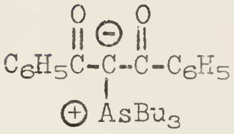
$NC-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-CO_2Et$

22



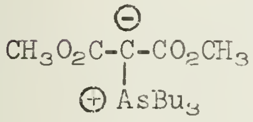
$EtO_2C-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-CO_2Et$

23



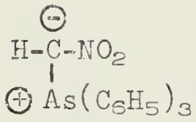
$C_6H_5\overset{O}{\overset{\|}{C}}-\underset{\oplus AsBu_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5$

24



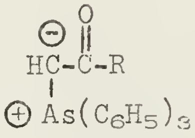
$CH_3O_2C-\underset{\oplus AsBu_3}{\overset{\ominus}{C}}-CO_2CH_3$

25



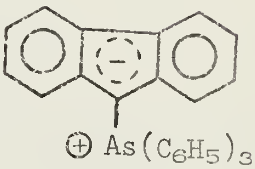
$H-\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-NO_2$

26



$H\underset{\oplus As(C_6H_5)_3}{\overset{\ominus}{C}}-\overset{O}{\overset{\|}{C}}-R$

27 a R = CH_3
b C_6H_5
c OEt
d p-$NO_2-C_6H_4$



28

Table 1. Reaction conditions and yields of ylides[20]

de	Carbon Acid employed	Yield, % ‘Arsine Oxide’ method + Ac_2O	+ P_2O_5/Et_3N	‘Carbene’ method (reaction temp, catalyst)
2	$Me_2\overset{\ulcorner CH_2CO \urcorner}{CH\cdot CH_2COCH_2}$	85	39	64(150°, CuBr)
3	$Me_2\overset{\ulcorner O\cdot CO \urcorner}{CH\cdot O\cdot CO\cdot CH_2}$	42	dec.	40(150°, CuBr)
4	$(PhCO)_2CH_2$	73	44	79(150°, CuBr)
5	Ac_2CH_2	33	48	34(150°, Cu)
6	$AcCH_2COPh$	27	44	54(150°, CuBr)
7	p-$NO_2C_6H_4COCH_2Ac$	35	no reaction	—
9	$(PhSO_2)_2CH_2$	52	—	96(150°, Cu)
8	$MeNO_2$	28	see 26	—
	$(NC)_2CH_2$	41	16	—
	$PhCOCH_2CO_2Et$	61	13	73(150°, CuBr)
	$AcCH_2CO_2Et$	68	22	56(120°, CuBr)
1	$AcCH_2CONHPh$	81	21	–
2	EtO_2CCH_2CN	89	72	–
3	$(EtO_2C)_2CH_2$	no reaction	no reaction	61(150°, Cu)
4	$(PhCO)_2CH_2$	dec.	33	–
5	$(MeO_2C)_2CH_2$	dec.	59	–
6	$MeNO_2$	see 18	64	–

analogous phosphorus ylide decomposes intramolecularly to give triphenylphosphine oxide.[21] This difference may be attributed to the strength of the P-O bond.

The unsubstituted cyclopentadienylide could not be obtained from triphenylarsine oxide and cyclopentadienyl magnesium bromide despite several attempts.[22] This ylide was finally prepared by allowing a solution of triphenylarsine and dibromocyclopentene to stand at room temperature for ten days. The salt obtained was treated with base and gave the desired ylide. When the reaction mixture was heated, no ylide was obtained.

REACTIONS WITH CARBONYLS

The most important application of arsonium ylides is their reaction with carbonyls to give olefins. Since arsonium ylides can react with carbonyls even if the ylide is stablized by two electron withdrawing groups, they offer a potential extension of the Wittig reaction.

The first attempts to use stabilized arsonium ylides in place of their phosphorus analogues were undertaken in the early 60's. A. W. Johnson, wanting to introduce disubstituted carbon at the 9-position of fluorene, examined the Wittig reaction as a possible synthetic route.[23] When triphenylphosphonium fluorenylide reacted well with benzaldehyde but failed to react with ketones, he attempted similar reactions with several substituted benzaldehydes. He also attempted reactions between the analogous arsonium ylide and substituted benzaldehydes. He rationalized his results (Table 2) on the basis of the higher positive charge on aldehyde carbonyl carbons than on ketone carbonyl carbon. He found that introduction of electron withdrawing groups on the phenyl ring clearly enhanced reactivity. Substitution of arsenic for phosphorus also increased reactivity although not enough, in this case, to obtain olefins from ketones. This work appears to be the basis for the widespread belief that aldehydes are more reactive than ketones toward stabilized arsonium ylides. Since Johnson attempted reactions with only two ketones, this is an unfortunate generalization.

Table 2. Yields of Alkenes from Fluorenyl Ylides[23]

	% Yield with	
Carbonyl	ϕ_3PFl	ϕ_3AsFl
Acetone	0	-
Acetophenone	-	0
Dimethylacetone dicarboxylate	0	-
Benzophenone	-	0
Cyclohexanone	0	-
Benzaldehyde	84	74
p-OMe	38	89
p-$(CH_3)_2N$	0	90
p-NO_2	96	92
p-Cl	-	98
Fluorenone	0	-
2,4,7-trinitro fluorenone	0	-
Acetaldehyde	-	91

The next attempts at extending the Wittig reaction by employing arsenic ylides were reported in 1971. Lloyd and Freeman[22] prepared triphenylarsoniumcyclopentadienylide by the reaction of dibromocyclopentene with triphenylarsine. They obtained the triphenylarsoniumcyclopentadienylide and attempted to react it with benzaldehyde, p-nitrobenzaldehyde and cinnaminaldehyde by heating to reflux in carbon tetrachloride. The ylide was consumed but instead of isolating fulvenes, they obtained dimers of the expected fulvenes. They next synthesized triphenylarsonium 2,3,4,5-tetraphenylcyclopentadienylide and triphenylarsonium 2,3,4-triphenylcyclopentadienylide as well as their phosphorus analogues. They added equimolar amounts of the tetraphenylcyclopentadienylides and benzaldehyde or p-nitrobenzaldehyde and heated to reflux in carbon tetrachloride for four to eighteen hours.[6,24] With the phosphorus ylides there is no reaction. With the arsonium ylides, the expected fulvenes were obtained in 16% and 95% yield respectively.

A similar situation prevails with the triphenylarsonium 2,3,4-triphenylcyclopentadienylides.[18] When the arsonium ylide is allowed to react with benzaldehyde or p-nitrobenzaldehyde, fulvenes are obtained in 35% and 92% yield respectively. There was no reaction with the corresponding phosphonium ylide.

Trippet and Walker[12] studied the reaction of substituted benzylidene triarylarsoranes with para-substituted benzaldehydes. As long as the arsonium ylides are stabilized by electron withdrawing groups, olefins and triphenylarsine oxide are obtained as the exclusive products. If there were no electron withdrawing groups on the ylide, epoxides were the only products (Table 3).

In May of this year, the synthesis of stabilized arsonium ylides 12-27 was reported[20]. Reaction of the ylides with benzaldehyde and p-nitrobenzaldehyde was attempted. Of the ylides with two electron withdrawing groups, only 23 reacts with benzaldehyde, forming the expected olefin in 72% yield. Although only one ylide is reactive, it is noteworthy because this is the only reported reaction between an ylide stabilized by two carbethoxy groups and a carbonyl group. Ylides 8,19-23, and 25-28 reacted with the more polar p-nitrobenzaldehyde to give alkenes in 39% to 96% yield (Table 4). The most strongly delocalized ylides are completely unreactive even with 2,4-dinitrobenzaldehyde. The ylides with only one electron withdrawing groups, 26, 27a-d, react with both benzaldehyde and p-nitrobenzaldehyde to give alkenes in 58% to 95% yield.

Table 3

Reactions of $Ar_3\overset{+}{A}s\cdot CH_2R^1$ with p-$R^2C_6H_4\overset{-}{C}HO$ in EtOH–EtONa at room temp.[12]

Ar	R^1	R^2	% Epoxide	% Olefin
Ph	Ph	H	90	
Ph	Ph	Cl	76	
Ph	Ph	OMe	56	
Ph	Ph	NO_2	75	
Ph	Ph	CN	87	
Ph	p-ClC_6H_4	H	51	
Ph	p-ClC_6H_4	NO_2	86	
Ph	p-$NO_2\cdot C_6H_4$	H		40
Ph	p-$NO_2\cdot C_6H_4$	NO_2		96
Ph	p-$CN\cdot C_6H_4$	H		67
Ph	H	H	87	
Ph	CO_2Et	H		77
p-$MeO\cdot C_6H_4$	Ph	NO_2	75	
p-$MeO\cdot C_6H_4$	p-$NO_2\cdot C_6H_4$	H		75
p-$MeO\cdot C_6H_4$	p-$NO_2\cdot C_6H_4$	NO_2		95

It is unfortunate that the authors did not attempt to react ylides 23 and 26 with ketones. The phosphorus analogues of these two ylides do not react with either aldehydes or ketones: the phosphorus analogue of 23 is completely unreactive while the phosphorus analogue of 26 is unstable and decomposes intramolecularly. Arsonium ylides 23 and 26 were proven reactive with aldehydes, yet ketones were not tested. If reactive with ketones, these ylides would significantly extend the scope of the Wittig reaction.

Table 4

Reactivities of ylides with aldehydes in refluxing solvents[20]

Ylide	Yield (per cent) of Olefin (solvent, reflux time) from benzaldehyde	from p-nitrobenzaldehyde
9,12→18	0	0
8	0	61 (dry benzene, 9 hr)
19	0	39 (CCl_4, 48 hr)
20	0	96 (CCl_4, 24 hr)
21	0	77 (benzene, 48 hr)
22	0	92 (CCl_4, 18 hr)
23	72 (CCl_4, 22 hr)	93 (CCl_4, 4 hr)
24	–	0
25	–	82 (CCl_4, 4 hr)
26	58 (benzene, 42 hr)	72 ($CHCl_3$, 24 hr)
27a	84 (benzene, 48 hr)	>95 (CCl_4, 10 min.)
27b	~90 (THF)	90 (benzene, 24 hr)
27c	90 (THF, 7 hr)	>95 (benzene, 10 min)
27d	77 (ethanol, 24 hr)	
28	74 ($CHCl_3$, 3 hr)	92 ($CHCl_3$, 3 hr)

Pyridinium[25 27], phosphonium[26] and sulfonium acylides react with diphenylcyclopropenone to give α-pyrones. Triphenylarsonium phenacylide, acetonylide and ethoxycarbonylmethylide all react with diphenylcyclopropenone to give 6-phenyl, 6-methyl, and 6-ethoxy 3,4-diphenylpyran-2-one in good yield. Ylides 15, 20 and 25 do not react.[20] The authors proposed initial attack on the ketone by the acyl oxygen rather than by carbon, although alternative mechanisms have been proposed.[28]

If α,β-unsaturated ketones with sterically hindered carbonyls are allowed to react with phosphonium ylides, the ylides attack at the beta position. When methylenetriphenylarsorane is allowed to react with benzylideneacetophenone or benzylidene-2',4',6'-trimethylacetophenone, cyclopropanes are formed through beta attack[12].

REACTIONS YIELDING CYCLOPROPANES

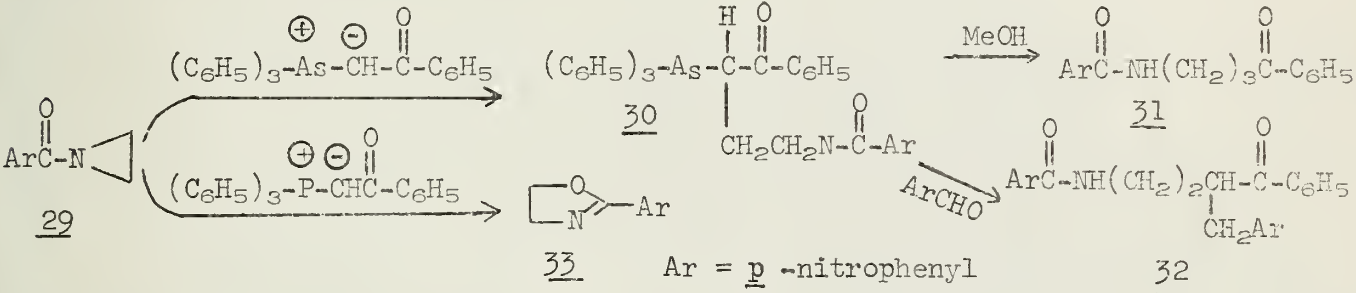
Johnson and Schubert[11] discovered that trans-1,2,3-tribenzoylcyclopropane was formed when a solution of triphenylarsonium phenacylide was heated in toluene. This is analogous to the behavior of the sulfonium ylide although the phosphonium ylide is stable to these conditions.

Nesmeyonov and Mikul'shina[29] allowed trans-dibenzoylethylene to react with triphenylarsonium phenacylide in order to determine whether arsonium ylides could replace sulfonium ylides which present experimental difficulty.[30] They obtained trans-tribenzoylcyclopropane (>90%) after chromatographic separation from starting materials. When the phenyl group was replaced by a methyl or methoxy group, isolated yields were lower because of the difficulty of separation from the original olefin.

REACTIONS WITH AZIRIDENES

The investigations of triphenylarsonium phenacylides prompted Heine and Wachob to study the reactions of this ylide, and its phosphorus analogue, with p-nitrobenzoylaziridene (29).[31] Triphenylarsonium phenacylide reacts with the aziridene to form N(γbenzoyl-γ-triphenylarsanyl propyl)-p-nitrobenzamide (30) in 65% yield (Scheme 4). A previous report of the formation of aziridenes from the reaction of Schiff bases with benzylidenetriphenylarsorane should be reexamined in view of this work. Triphenylphosphonium phenacylide does not react with the aziridene under identical conditions, but instead catalyzes the rearrangement of the aziridene to the oxazoline 33.

Scheme 4


$(C_6H_5)_3\overset{\oplus}{As}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-C_6H_5$
$(C_6H_5)_3-As-\overset{H}{C}-\overset{O}{\overset{\|}{C}}-C_6H_5$
MeOH
$ArC(=O)-NH(CH_2)_3C(=O)-C_6H_5$
$ArC(=O)-N$
29
$(C_6H_5)_3-\overset{\oplus}{P}-\overset{\ominus}{C}HC(=O)-C_6H_5$
30
$CH_2CH_2N-C(=O)-Ar$
31
ArCHO
$ArC(=O)-NH(CH_2)_2CH(CH_2Ar)-C(=O)-C_6H_5$
O
N
Ar
33
Ar = p -nitrophenyl
32

Summary

Arsonium ylides have been prepared by a variety of reactions and proven to be reactive in specific cases with aldehydes. It is difficult to estimate the synthetic importance of these ylides because there is little data available on their reactivity with ketones. At a minimum, the reactivity of ylides 23 and 26 toward ketones should be determined. More information on the reactivity of the other stabilized ylides would be highly desirable.

At present, ylides 23 and 26 increase the utility of the Wittig reaction significantly. Alkyl derivatives of 26 should prove at least as reactive and ought to be examined. Arsonate-derived ylides have not been examined but should be, since they may offer additional advantages.

BIBLIOGRAPHY

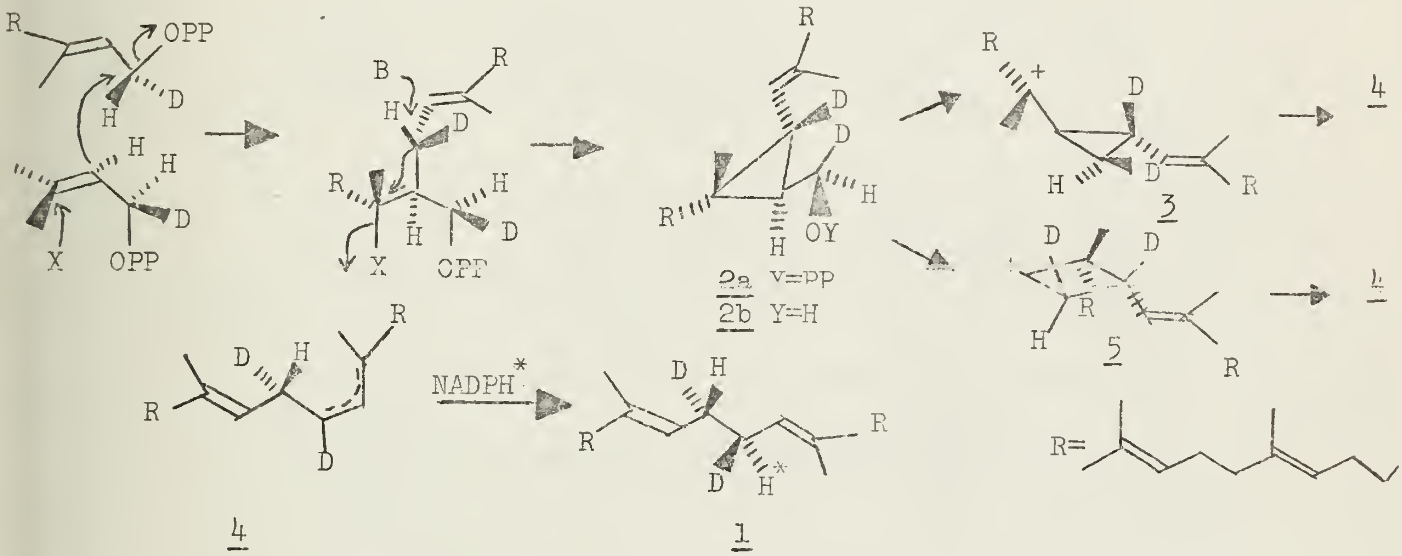
1. A. Michaelis, Ann., 321, 174 (1902).
2. G. O. Doak and L. D. Freedman, Organomet. Chem. Rev., 8, 171 (1971).
3. D. J. Cardin, M. F. Lappert, J. D. Smith and D. R. M. Walton, Ann. Rep. Prog. Chem., 67, 271 (1970).
4. A. W. Johnson, "Ylide Chemistry", New York: Academic Press (1966).
5. For leading references see: A. Maerker, Organic Reactions, 14, 270 (1965); S. Trippet, Quart. Rev. (London), 17, 406 (1963); G. Wittig, Pure Appl. Chem., 9, 245 (1964).
6. B. H. Freeman, D. Lloyd and M. I. C. Singer, Tetrahedron, 28, 343 (1971).
7. L. Horner, H. Hoffman, and H. Wippel, Chem. Ber., 91, 61 (1958).
8. A. W. Johnson and R. B. LaCount, Tetrahedron, 9, 130 (1960).
9. P. Frøyen, Acta. Chem. Scand. 25, 2541 (1971).
10. N. Nesmeyanov. V. Mikul'shina and O. A. Reutov, J. Organomet. Chem., 13, 67 (1968).
11. A. W. Johnson and H. Schubert, J. Org. Chem., 35, 2678 (1970).
12. S. Trippet and M. A. Walker, J. Chem. Soc. (C), 1114 (1970).
13. F. Krohnke, Chem. Ber., 83, 291 (1950); G. Wittig and H. Laib, Ann., 580, 57 (1953); S. O. Grim and D. Seyferth, Chem. Ind., 849 (1959); M. C. Henry and G. Wittig, J. Am. Chem. Soc., 82, 563, (1960); N. A. Nesmeyanov, V. V. Pravdina and O. A. Reutov, Doklady Akad. Nauk. S.S.S.R., 155, 1364 (1964).
14. D. Lloyd and I. Gosney, umpublished data (quoted in ref. 20).
15. L. Horner, Chem. Ber., 91, 437 (1958); Ann. 627, 142 (1959).
16. D. Lloyd and M. I. C. Singer, Chem. Ind., 510 (1967).
17. B. H. Freeman, G. S. Harris, B. W. Kennedy, and D. Lloyd, Chem. Comm., 912 (1972).
18. D. Lloyd and M. I. C. Singer, J. Chem. Soc. (C), 2941 (1971).
19. G. S. Harris and D. Lloyd, Chem. Ind., 787 (1967), and ref. 18.
20. I. Gosney and D. Lloyd, Tetrahedron, 29, 1697 (1973).
21. S. Trippet and D. M. Walker, J. Chem. Soc. 3874 (1959).
22. B. H. Freeman and D. Lloyd, J. Chem. Soc. (C), 3164 (1971).
23. A. W. Johnson, J. Org. Chem., 25, 183 (1960); and 24, 284 (1959).
24. D. Lloyd and M. I. C. Singer, Tetrahedron, 28, 353 (1972).
25. T. Eicher, E. von Angerer and A. Hansen, Ann., 746, 102 (1967).
26. T. Eicher and A. Hansen, Tetrahedron Letters, 1169 (1967).
27. T. Sasaki, K. Kanematsu, and A. Kakehi, J. Org. Chem., 36, 2451 (1971).
28. Y. Hayasi and H. Nozaki, Tetrahedron, 27, 3085 (1971).
29. N. A. Nesmeyanov and V. Mikul'shina, Russ. J. Org. Chem., 706 (1971).
30. J. C. Block, Ann. Chim., 10, 419 (1965); H. Nozaki, M. Takaku, and K. Kondo, Tetrahedron, 22, 2145 (1966); B. M. Trost, J. Am. Chem. Soc., 89, 138 (1967).
31. H. Heine and D. Wachob, J. Org. Chem., 37, 1049 (1972).
32. E. Ciganek, J. Org. Chem., 35, 1726 (1970).

THE MECHANISM OF HEAD-TO-HEAD TERPENE BIOSYNTHESIS

Reported by David Ley September 27, 1973

Although the mechanism of head-to-tail terpene biosynthesis (prenyl transfer) has been understood for some time,[1,2] the course of the biosynthesis of squalene from farnesyl pyrophosphate has been particularly controversial and elusive. Squalene (1) is biosynthesized by an unsymmetrical process in which two farnesyl moietes contribute unequally to each half of the molecule. It is known that one hydrogen on the C_1 carbon of one farnesyl residue is stereospecifically replaced by a hyride from NADPH and inversion of configuration occurs at the C_1 carbon of the second farnesyl residue.[3]

In 1966, Rilling[4] isolated a new squalene precursor. His discovery was confirmed by other workers[5,6] and several structures were proposed for the intermediate.[4,5,6] After his first structure was proven incorrect,[8] Rilling proposed 2a as the structure of the intermediate.[7] Three groups independently synthesized 2b[9,10,11] and in each case the pyrophosphorylated compound 2a was converted into squalene. In addition, exhaustive degradative studies and stereochemical investigations have been carried out on the natural intermediate.[12,13,14] Their results support 2a as the structure of presqualene.



Several pathways have been proposed for the formation of presqualene. One involves activation of C_2 of one farnesyl residue which results in nucleophilic attack at C_1 of the second farnesyl residue. This is followed by a trans 1,3-elimination of the activating group and a proton to form 2a.[7,12,13] Alternatively, after the nucleophilic attack at C_1, the C_2-C_3 double bond isomerizes to the C_1 position. The resulting homoallylic system ring closure is accompanied by proton elimination.[15,16]

The enzyme mediated cleavage of the cyclopropyl ring to form squalene has been a topic of great interest.[7,10,12,13,16] Simple cleavage of the cyclopropyl ring cannot account for this conversion. In this system, cleavage of any of the ring bonds leads to a known acyclic terpene skeleton.[17] Two related pathways have been proposed for the transformation of presqualene to squalene. Elimination of the pyrophosphate group could be accompanied by a cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement utilizing the C_3-C_4 bonding electrons to yield the tertiary cyclopropylcarbinyl cation (3) which collapses to an allylic carbonium ion (4) which is stereospecifically reduced to squalene.[7,12] Ample precedent exists for

each of these steps.[18,19] The other proposal[10,13,15,16] involves ionization accompanied by ring-expansion using the C_2-C_4 bond to afford a cyclobutylcarbonium ion (5) (or equivalent nonclassical bicyclobutonium ions) which collapses to 4 followed by reduction to squalene. Both pathways account for the known stereochemistry of squalene and are chemically precedented.[19] Strong support for these mechanisms comes from work on model systems which mimic this conversion.[20,21]

The recent discovery of "prephytoene" an analog of presqualene, suggests that this may be a general mechanism in head-to-head terpenoid condensations.[22,23] There is some controversy at this time whether "prephytoene" is converted directly to phytoene. It has been suggested that lycopersene is formed first and is dehydrogenated to form phytoene.[23] This pathway follows the known conversion of presqualene to squalene.

In the light of this new knowledge, a unified scheme has been suggested for the formation of several irregular monoterpenes found in the Compositae family.[24] However at this time there is no experimental evidence to support the scheme.

REFERENCES

1. R. B. Clayton, Quart. Rev. Chem. Soc., 19, 168 (1965).
2. J. W. Cornforth, Angew. Chem. Int. Ed. Engl., 7, 903 (1968).
3. G. Popjak and J. W. Cornforth, Biochem. J., 101, 553 (1966).
4. H. C. Rilling, J. Biol. Chem., 241, 3233 (1966).
5. G. Popjak, J. Edmond, R. Clifford, and V. Williams, ibid., 244, 1897 (1969).
6. H. Wasner and F. Lyman, Fed. Eur. Biochem. Soc. Lett., 12, 54 (1970).
7. W. W. Epstein and H. C. Rilling, J. Biol. Chem., 245, 4597 (1970).
8. E. J. Corey and P. H. Ortiz de Montellano, Tetrahedron Lett., 5113 (1968).
9. R. V. M. Campbell, L. Crombie, and G. Pattenden, Chem. Commun., 218 (1971).
10. L. J. Altman, R. C. Kowerski, and H. C. Rilling, J. Amer. Chem. Soc., 93, 1782 (1971).
11. R. M. Coates and W. H. Robinson, ibid., 93, 1785 (1971).
12. H. C. Rilling, C. D. Poulter, W. W. Epstein, and B. Larsen, ibid., 93, 1783 (1971).
13. J. Edmond, G. Popjak, S-M. Wong, and V. Williams, J. Biol. Chem., 246, 6254 (1971).
14. G. Popjak, J. Edmond, and S-M. Wong, J. Amer. Chem. Soc. 95, 2713 (1973).
15. E. Beytia, A. A. Qureshi, and J. W. Porter, J. Biol. Chem., 248, 1856 (1973).
16. E. E. van Tamelen and M. A. Schwartz, J. Amer. Chem. Soc., 93, 1780 (1971).
17. L. Crombie, P. A. Firth, R. P. Houghton, D. A. Whiting, and D. Y. Woods, J. Chem. Soc., Perkin I, 642 (1972), and references therein.
18. C. D. Poulter, E. C. Friedrich, and S. Winstein, J. Amer. Chem. Soc., 92, 4274 (1970).
19. K. B. Wilberg, A. H. Hess, Jr., and A. J. Ashe, III, in "Carbonium Ions," Vol. III, G. A. Olah and P. V. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, pp. 1295-1345.
20. R. M. Coates and W. H. Robinson, J. Amer. Chem. Soc., 94, 5920 (1972).
21. C. D. Poulter, O. J. Muscio, C. J. Spillner, and R. G. Goodfellow, ibid., 94, 5921 (1972).
22. L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, ibid., 94, 3257 (1972).
23. A. A. Qureshi, F. J. Barnes, and J. W. Porter, J. Biol. Chem., 247, 6730 (1972).
24. W. W. Epstein and C. D. Poulter, Phytochemistry 12, 737 (1973).

RECENT STUDIES ON ASYMMETRIC REDUCTIONS

Report by Richard W. Thomas October 1, 1973

INTRODUCTION

While the field of asymmetric synthesis has been widely studied in the past two decades,[1] it is still a relatively undeveloped area. Most of the emphasis has been placed on finding new reagents and running test reactions. Unfortunately, many of these reagents have yet to be explcited in actual synthetic schemes. Until this is successfully done, the true value of these reagents cannot be fully realized. Studies on asymmetric synthesis are potentially of great importance since almost all natural products are asymmetric and in most cases, only one of the enantiomers is biologically active. One area where asymmetric syntheses have been particularly useful is in the preparation of optically active amino acids.[2]

Broadly defined, an asymmetric synthesis is a reaction in which an achiral substrate is converted by a chemical reagent, catalyst, solvent, or physical force such as circularly polarized light, into a chiral molecule in such a manner that the stereoisomeric products, either enantiomeric, or diastereomeric, are formed in unequal amounts. A majority of the work to date is concerned with the asymmetric reductions of carbonyls, olefins and imines. This paper is intended to review the recent work on these types of reactions.

METAL HYDRIDE REDUCTIONS

The use of optically active lithium aluminum hydride (LAH) complexes began in 1951, when Bothner-By[3] reported that reduction of butanone and methyl t-butyl ketone with LAH in the presence of (+)-camphor afforded optically active alcohols. Unfortunately, it was later discovered that the activity was due to residual camphor, but when it was shown by Haubenstock and Eliel[4] that low selectivity could be obtained, LAH reductions were studied further.

Kretchmer[5] has described the reduction of several ketones to optically active alcohols using (+)-tris((S)-2-methylbutyl) aluminum etherate. The results are shown in Table I.

Table I

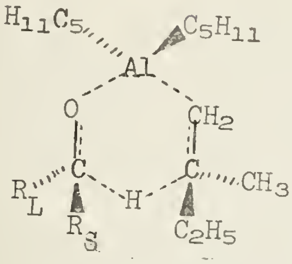
Ketone	Alcohol	Yield %	Conf	Opt. Purity[s] %
acetophenone	methylphenylcarbinol	83	S	8
isobutyrophenone	i-propylphenyl "	93	S	30
n-butyrophenone	n-propylphenyl "	97	S	7
3,3-dimethyl-2-butanone	t-butylmethyl "	-	R	13

The results are rationalized via a six-membered transition state shown in Figure I which is often invoked in aluminum hydride reductions. R_L and R_S represent large and small groups respectively. Reasoning that the phenyl group (R_L in the firs three cases) should be as far removed from the bulkier ethyl group as possible, one can rationalize the formation of an excess of the S isomer. Unfortunately, the dialkyl case gives anomolous results which could not be explained by the model. Evidently, factors beside steric effects are playing a role.

Using the chiral organometallic complexes, tris-((S)-3-methylpentyl)-aluminum, bis-((R)-2-methylbutyl)beryllium, Kretchmers' reagent described above[5] and chiral solvates of tris-isobutyl aluminum, Giacomelli and Lardici[7] have

Figure I

Transition State for Tris((S)-2-methylbutyl)aluminum - Ketone Reduction



studied the reduction of alkyl phenyl ketones and dialkyl ketones obtaining values comparable with those of Table I. Their results are summarized in Table II.

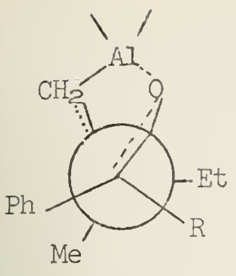
There are several mechanistic implications that can be drawn from Table II. Kretchmer's model for asymmetric induction was based on bulk effects at the chiral β-carbon. In the reactions (4-6) where tris((S)-3-methylpentyl)aluminum was used, which has its chirality at the γ-position, induction is still observed. Here it is postulated[7b] that an asymmetric center at the γ-position controls the chirality of the β-carbon in the transition state and consequently that of the incipient asymmetric carbinol atom. All carbinols have the S absolute congriguration with the extent of asymmetric reduction dependent on the nature of the alkyl group of the ketone, increasing $CF_3 \cong Me < Et < t\text{-}Bu < i\text{-}Pr$. This is consistent with the cyclic, six-membered model except for the position of t-Bu and the reversed configuration for the -CF_3 carbinol. Giacomelli proposes four possible configurations in the transition state (I-IV). I and II lead to S-carbinol, III and IV to R-carbinols. Nasipuri[8] in an earlier communication had theorized that electronic factors in the transition state were as important as steric considerations. By placing the CH_2-Al$^{\delta+}$ dipole between the C-O$^{\delta-}$ and C-Ph$^{\delta-}$ dipoles, the transition state is stabilized. Along with steric considerations, I becomes the favored state. As R is increased in bulk, the mobility of the phenyl ring decreases, and of the two competing, electronically favored states I and IV,

Table II

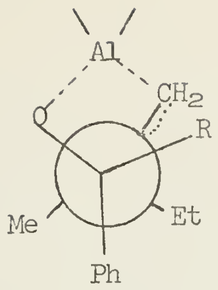
Reduction of RCOR' with Various Metal Hydrides

React.	R	R'	Yield	Config.	Opt. Purity (%)
Bis-((R)-2-methylbutyl)beryllium					
1.	Et	Ph	88.5	S	5.4
2.	i-Pr	Ph	97.5	S	16.8
3.	t-Bu	Ph	90.5	S	11.2
Tris-((S)-3-methylpentyl)aluminum					
4.	t-Bu	Me	82	S	9.2
5.	Et	Ph	63	S	10.1
6.	i-Pr	Ph	70	S	14.9
Tris-((S)-2-methylbutyl)aluminum					
7.	Me	Ph	87	S	6
8.	Et	Ph	98	S	13
9.	i-Pr	Ph	96	S	44
10.	t-Bu	Ph	98.1	S	30
11.	CF_3	Ph	100	S	6

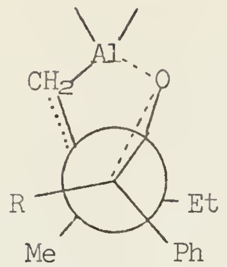
All reductions we carried out in pentane solution using equimolar amounts of ketone and organometallic.



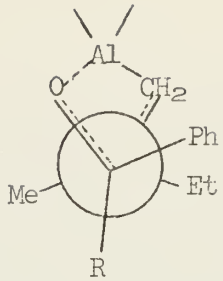
I



II



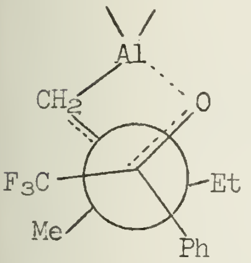
III



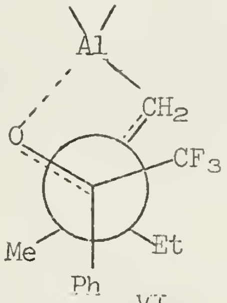
IV

(viewed along the C···H-C* bond)

IV is more hindered, so the amount of S alcohol should increase. The decrease from i-Pr to t-Bu might be due to the inability of torsional and angular strain to diminish compressions thereby helping equilize I and IV. The anomalous behavior of CF$_3$ is explained by assuming that the most favorable transition state places the CH$_2$-Al$^{\delta+}$ dipole between the C-O$^{\delta-}$ and C-CF$_3$$^{\delta-}$ dipole. The two possibilities are V, leading to the S isomer, and VI, leading to the R isomer. Of these two, V is the most stable for steric reasons. When phenyl is replaced by groups of comparable size (e.g. cyclohexyl or t-butyl) but without significant electronic effect, the optical purity of the carbinol drops off as transition states corresponding to III and II become significant.

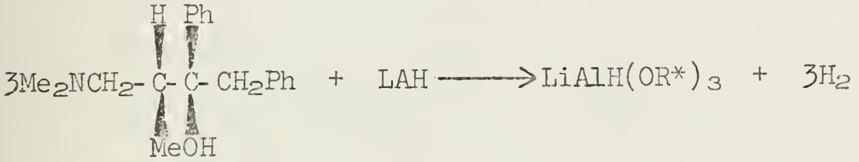


V



VI

Yamaguchi and Mosher[9] discovered an interesting phenomenon while investigating the reaction of acetophenone by the chiral reagent formed from addition of an ether solution of 2-3 equivalents of (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (VII) to a solution of LAH. If the acetophenone was reduced within ten minutes of preparation of VIII, R-(+)-phenylethanol was formed in up to 75% optical yield, while after ten minutes, the S-(-) isomer was formed in up to 66% optical yield. While the authors could give no definative explanation, it



$$3Me_2NCH_2-\overset{H}{\underset{Me}{C}}-\overset{Ph}{\underset{OH}{C}}-CH_2Ph \quad + \quad LAH \longrightarrow LiAlH(OR^*)_3 \quad + \quad 3H_2$$

VII VIII

was felt that both homogeneity and degree of aggregation were involved since the initially heterogeneous system became homogeneous upon standing.

Asymmetric reductions have recently been carried out with LAH modified with (-)-menthol,[10] (-)-quinine,[11] and optically active sugars.[12,13] The best results were obtained using LAH modified with (-)-menthol to reduce a series of β-amino ketones. Using three equivalents of (-)-menthol to one equivalent of LAH, optical yields as high as 73% of the corresponding alcohol have been obtained. Less successful were reductions using LAH complexes with sugars. Only a 5.7% excess of the R alcohol was obtained when acetophenone was reduced with a 1:1 complex of LAH and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose in

ether.[12] Giacomelli[7c] has reported optical yields of 1-8% for the reduction of alkyl phenyl ketones with trisisobutylaluminum in the presence of chiral molecules such as (-)-sparteine, (+)-(S)-sec-BuOEt and (+)-(3S,1S)-3-sec-BuTHF.

Grundon et. al.[14] has described the preparation of lithium alkyl(hydro) dipinan-3α-ylborates (IX) for use as reducing agents for dialkyl ketones and imines. Pinan-3α-yl boranes are known to react with olefins,[15] being a well founded method for the preparation of optically active alcohols. Using methylhydroborate prepared from (-)-pin-2-ene, a series of dialkyl ketones were reduced to the corresponding alcohols. Optical yields were generally below 10% except for ethyl isopropyl ketone which yielded a 46% excess of the S alcohol. Of greater interest are the studies on imine reduction with IX since it is a potentially important route to optically active alkaloids. To test the reagent, a series of 2-alkylsubstituted 3,4,5,6-tetrahydropyridines were

$$R'_2BH + R''Li \longrightarrow R'_2BR''HLi \qquad \text{IX}$$

R'=pinan-3α-yl $\qquad$ R''=n-butyl or methyl

reduced to the corresponding piperidines.

When IX was prepared from (+)-α-pinene, the (R)-2-alkylpiperidine was formed in excess, and when (-)-α-pinene was used, the S isomer was found to be in excess. The results of these experiments are shown in Table III. To explain the results, the authors invoked the transition state shown in IIB. The smaller the group R''', the greater will be the disparity in size between it and the ring carbon atoms, and therefore the induced chirality should be greater. This is observed. The effect of R" is not well understood.

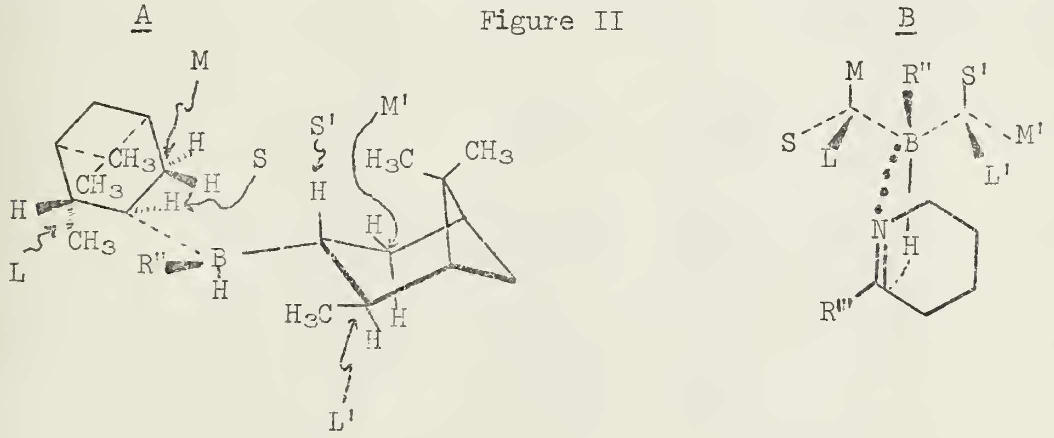
Table III

Imine reductions with lithium alkyl- or phenyl-(hydro)-dipinan-3-α-ylborate

R'''	R''		Yield(%)	Opt. Yield(%)	Config.
Me	n-Bu	a	37	25	R
Me	n-Bu	b	32	22	S
Me	Ph	a	32	10	R
Me	Ph	b	30	10	S
Et	n-Bu	a	48	5	R
n-Pr	n-Bu	a	75	4	R
n-Pr	Me	a	82	11	R

(a) reagent prepared from (+)-α-pinene
(b) reagent prepared from (-)-α-pinene

Figure II



Alkyl dipinan-3α-ylborane $\qquad$ Imine Transition State

S=Small $\qquad$ M=medium $\qquad$ L=large

Asymmetric induction in the reduction of imines formed by reaction of optically active α-phenylethylamine and dialkyl ketones, by LAH, diborane and $Pd(OH)_2/C$ has been reported by Charles.[16] Evidently the chiral center is able to direct the steric course of the reaction to the extent of up to 60% for B_2H_6, 25% for LAH and 56% for $Pd(OH)_2/C$.

Using $LiAl(O\text{-}t\text{-}Bu)_3H$, Yamaguchi[17] has observed small optical yields in the reduction of chiral, α-ketoesters. Optical yields of between 8 and 13% of the R,S isomer have been obtained, an apparent violation of Prelog's Rule which predicts an excess of the S,S isomer.

REDUCTION WITH OPTICALLY ACTIVE GRIGNARD REAGENTS

While reaction of carbonyls with Grignard reagents usually leads to addition,[18] there are examples of ketone reductions with Grignard reagents prepared from optically active halides producing optically active secondary alcohols. The most recent[19] is a report of the reaction of phenyl trimethylsilyl ketone and phenyl triphenylsilyl ketone with $CH_3CH_2CH(CH_3)CH_2MgCl$ (**X**), and $CH_3CH_2CH(C_6H_5)CH_2MgCl$ (**XI**). Optical yields were on the order of 10% using **X** and 30% using **XI**. The results were explained using a cyclic six-membered transition state, similar to Fig. I. The greatest asymmetric induction occurs with **XI** where the mutual repulsion of the electron rich π-cloud of the benzene rings forces them into opposite positions. With reagent **X**, the bulk and steric factors aren't as important, so the optical yields are lower.

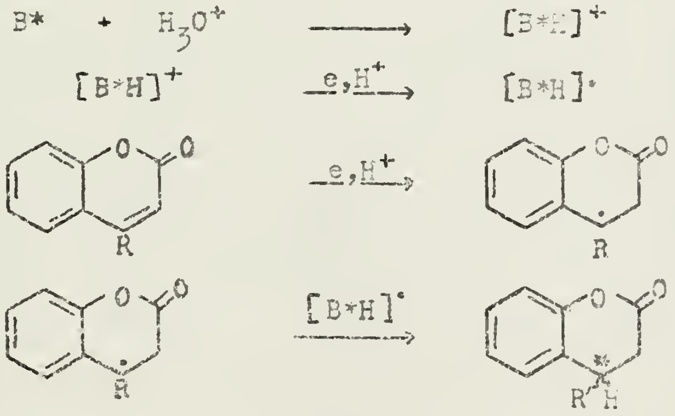
ELECTROCHEMICAL ASYMMETRIC REDUCTIONS

In attempts to produce optically active compounds, electrosynthesis is a promising technique since it involves a heterogeneous surface reaction that can be controlled by the proper choice of the potential, electrode material, etc. Many alkaloids which are available from natural sources in optically active form are electrosorbed to a large extent on mercury and can be used to impart asymmetry at the electrode surface.

Gourely[20] has studied the electroreduction of coumarin derivatives on mercury cathodes in the presence of several alkaloids. With reduction occuring across the 4,5 double bond, a mixture of monomer and dimer was obtained. As the concentration of alkaloid was increased, the amount of monomer increased. The alkaloids used were known to cause catalytic hydrogen evolution on mercury in the same potential range in which coumarins are reduced. This led Gourely to propose a mechanism in which asymmetry was imparted via a hydrogen transfer from the asymmetric alkaloid. (Scheme I) Using 4-methyl coumarin as a substrate, optic yields for the various alkaloids were: sparteine-17%; narcotine-15%; emetine-12%; and codeine-12%.

Scheme · I

Electroreduction of Coumarins in the Presence of Optically Active Alkaloids (B*)

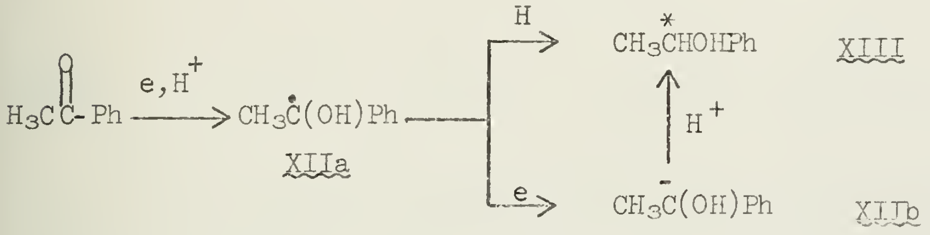


Horner at. al.[21] studied the electrochemical reduction of several ketones and imines in the presence of chiral, electrochemically inert electrolytes (ephedrine, asymmetric tertiary amines and quarternary ammonium salts). He found that as the concentration of amine increased, the induced asymmetry of the products increased, presumably due to the asymmetric environment created in the near vacinity of the electrode. Due to the inertness of the alkaloids in the potential range employed, he could not propose a mechanism like that of Gourely. Optical yields were generally low, being on the order of 0 to 10%.

A final study[22] involved the electroreduction of acetophenone in the presence of quinidine. As with the coumarins, a mixture of monomer and dimer was produced. The mechanism of acetophenone reduction is known to follow the path shown in Scheme II. To obtain chiral alcohol, either XIIa or XIIb is adsorbed in a well defined orientation due to the presence of the alkaloid, or the adsorbed alkaloid transfers a hydrogen atom or proton to the appropriate intermediate. Due to the low surface coverage at moderate alkoloid concentrations, the latter suggestion is most likely. The highest optical yield obtained with quinidine was 15%.

Scheme II

Electrochemical Reduction of Acetophenone



CATALYTIC HYDROGENATION

Enantioselective catalytic hydrogenation has been reviewed through 1970 by Izumi.[1b] He and his coworkers have contributed extensively in this field, especially in the use of modified Raney nickel. They found that Ra-Ni, modified with optically active amino or hydroxy acids would induce asymmetry in the hydrogenation of certain ketones and olefins.[23] In later studies they showed that the modifying reagent has to be optically active, and preferably have one carboxyl group, an amino or a hydroxyl group, and a hydrogen at the chiral center. β-Diketones and β-keto esters are the best substrates which leads to the conclusion that the adsorption of the carbonyl groups on the catalyst surface to form a chelate structure is an important factor in the hydrogenation. Recent papers[24] have centered on the structural requirements of the modifying reagent. Izumi[24a] has shown that substituting α-amino alcohols for α-aminoacids, considerably depresses the asymmetric activity. This was attributed to the low adsorption stability of the catalyst after contact with substrate. In a companion paper, Harada,[24b] using 3-methylglutamic acid and 2-aminotricarballylic acid, showed that while the configuration of the α-carbon controls the direction of reduction, the bulk and electronics of substituents on the β-carbon greatly affect the extent of the induced asymmetry. The amino group seems to play an important role in the asymmetric control of the substrate approaching the catalyst surface since N-acetylation of several modifying reagents didn't greatly affect the adsorption stability, but did reduce the induced asymmetry.[24c] In their latest report, Tanabe and Izumi[24d] have reported optical yields of up to 66% for the reduction of β-keto esters by Ra-Ni modified with D-tartaric acid making this an attractive synthetic procedure. In general, optical yields are not very high, and until the method is extended to more complex systems, it is not terribly useful.

The use of chiral phosphine-rhodium and platinum complexes has met with limited success in the last several years. Morrison[25] has prepared tris(neomenthyldiphenylphosphine)rhodium chloride (NMDPP) and found it to be a very good catalyst for the homogeneous hydrogenation of α,β-unsaturated carboxylic acids. (E)-β-methylcinnamic acid was reduced with NMDPP to give a 61% excess of S-3-phenylbutanoic acid; (E)-α-methylcinnamic acid gave a 52% excess of R-2-methyl-3-phenylpropanoic acid; and atropic acid yielded a 28% excess of S-hydratropic acid. α-Ethylstyrene was reduced in only 7% yield implicating the carboxylate group in possible coordination with rhodium.

Bonvicini[26] has had moderate success in the reduction of acetophenone and 2-butanone using bis(benzylmethylphenylphosphine)-1,5-norbornadiene rhodium perchlorate. He obtained 8.6% optical yield of R-(+)-1-phenylethanol and 1.9% optical yield of R-(-)-2-butanol. Horner and Siegel[27] have studied the reaction of α-substituted styrenes with chiral rhodium complexes prepared from rhodium chloride-1,5-hexadiene and chiral tertiary phosphines (Scheme II). The optical yield of the products ranged from 2 to 19%. A direct relationship (R to R and S to S) between the absolute configuration of phosphine and the product was observed.

Scheme III

$$C_6H_5(X)C{=}CH_2 \; + \; \xrightarrow[H_2]{RP(XH_3(C_6H_5)YP)_2(1,5\text{-hexadiene})Cl} C_6H_5\overset{*}{C}XHCH_3$$

X=Et, Pr, C_7H_7, α-$C_{10}H_7$, OCH_3, Br

Y=n-C_3H_7(R- and S-), i-C_3H_7(R- and S-), n-C_4H_9(R- and S-), t-C_4H_9(R-).

Using chiral platinum-phosphine[28a] and rhodium-phosphine,[28b] Yamamoto has observed asymmetric hydrosilylation of a series of phenyl alkyl ketones. His results are summarized in Table IV. In reaction series 2b. PhCO-tBu gave anomalous results. The use of the bulkier silane in (2a) gave the best results as did the bulkier alkylphenyl ketones.

Table IV

Asymmetric Hydrosilylation of Ketones by Chiral Phosphine-Metal Complexes

Ketone		Carbinol Conf.	Opt. Yield
1. $[((R)\text{-}(+)\text{-}(PhCH_2)MePhP)PtCl_2]_2$	$(MeCl_2SiH)$		
PhCOMe	81	S	7.6
PhCOEt	81	S	10.0
PhCO-nPr	77	S	8.4
PhCO-iPr	55	S	4.5
PhCO-tBu	33	S	18.6
2. $((R)\text{-}(+)\text{-}(PhCH_2)MePhP)H_2Rh^+ClO_4^-$			
(a) $PhMe_2SiH$			
PhCOMe	97	S	31.6
PhCOEt	94	S	43.1
PhCO-tBu	84	S	61.8
(b) Me_3SiH			
PhCOMe	100	S	5.1
PhCOEt	92	S	6.4
PhCO-tBu	81	R	28.1

Note: the optical yields are determined after methylation with MeLi followed by acid hydrolysis of the silane.

Ohgo[29] has prepared several optically active cobalt(II) complexes using R(-)-1,2-propanediamine, S(+)-dimethyl-1,2-propanediamine and dimethylglyoxime in the presence of quinine.

Quinine is used in the later case to induce asymmetry in the dimethylglyoxime ring. He reasoned that a polyfunctional asymmetric substance, bound to a ligand, could draw the substrate into the reaction center with a weakly attractive force. These complexes have been used to cataltze the hydrogenation of active olefins, nitro, azoxy, azobenzenes, α-diketones, and α-keto carboxylic acids with moderate success, the optical yields generally being below 10%. However, using $Co(DMG)_2$-quinine, S(+)-benzoin was obtained from benzil in 61% optical yield.

Heterogeneous hydrogenation with Pd/C in the presence of the optically active organic bases l-sparteine, l-ephedrine, S- and R-α-methylbenzylamine, R-(+)-α-ethylbenzylamine and S- and R-α-(1-naphthyl)ethylamine, has been used to reduce several organic acids.[30] Benzaldehyde, 2-acetamidoacrylic acid, 1-phenyl-2-acetamidoacrylic acid and 2-benzylpyruvic acid were reduced in 5 to 10% optical yield. It was found that both the direction and extent of the asymmetric reduction were highly dependent on the dielectric constant of the solvent. Further work is required to elucidate the mechanism of this and many of the previously mentioned hydrogenations.

BIBLIOGRAPHY

1. This subject has been reviewed. (a) For a complete review of the literature through 1969, see, J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Englewood Cliffs, N. J. Prentice Hall Inc. (1971). (b) For a review on asymmetric catalytic hydrogenation see, Y. Izumi, Angew. Chem. Int. Ed., 10, 871 (1971). (c) For a short review on asymmetric synthesis see, T. D. Inch, Synthesis, 466 (1970). (d) For a review of asymmetric hydride reductions, see S. Yamada and K. Koga in "Selective Organic Transformations", B. S. Thyagarajan, Ed., 1, 1 (1970).
2. L. G. Dammann, Org. Sem. Abst., 65 (1970).
3. A. A. Bothner-By, J. Amer. Chem. Soc., 73, 846 (1951).
4. H. Haubenstock and E. L. Eliel, ibid., 84, 2363 (1962).
5. R. A. Kretchmer, J. Org. Chem., 37, 801 (1972).
6. In all cases, optical purity is the percent excess of one enantiomer over the other.
7. (a) G. P. Giacomelli et.al., Tetrahedron Lett., 4135 (1971). (b) L. Lardicci et.al., ibid., 687 (1972). (c) G. P. Giacomelli et.al., J. Org. Chem., 38, 2370 (1973).
8. D. Nasipuri et.al., Tetrehedron Lett., 1587 (1971).
9. (a) S. Yamaguchi and H. S. Mosher, J. Amer. Chem. Soc., 94, 9254 (1972). (b) S. Yamaguchi and H. S. Mosher, J. Org. Chem., 38, 1870 (1973).
10. R. Andrisano et.al., Tetrahedron, 29, 913 (1973).
11. (a) O. Cervinka and O. Kruz, Collect. Czech. Chem. Commun., 38, 284, 441 (1973). (b) O. Cervinka et.al., Z. Chem., 11, 11 (1971).
12. O. Cervinka and A. Fabryova, Z. Chem., 9, 426 (1969).
13. S. R. Landor et.al., J. Chem. Soc., Sec. C, 2339 (1971).
14. (a) M. F. Grundon et.al., ibid., 2557 (1971). (b) J. F. Archer et.al., ibid., 2560 (1971).
15. H. C. Brown et.al., J. Amer. Chem. Soc., 86, 399 (1964).
16. (a) J-P. Charles et.al., Bull. Soc. Chim. Fr., 1124 (1972). (b) J-P. Charles, ibid., 4439 (1970).
17. S. Yamaguchi et.al., J. Org. Chem., 37, 3174 (1972).

18. Grignard additions to carbonyls are used extensively in asymmetric synthesis. The achiral reagents are often modified with optically active alkaloids or sugars. For recent papers see, R. Kretchmer, J. Org. Chem., 37, 2744, (1972), H. Nozaki et.al., Tetrahedron, 27, 905, (1971), and T. D. Inch et.al., Tetrahedron Lett., 3657 (1969).
19. M. S. Biernbaum and H. S. Mosher, J. Org. Chem., 36, 3168 (1971).
20. R. Gourely et.al., J. Chem. Soc., Sec. C, 2318 (1970).
21. (a) L. Horner et.al., Tetrahedron Lett., 1241, 1245 (1971). (b) L. Horner et.al., Chem. Ing. Tech., 44, 209 (1972).
22. E. Kariv et.al. Electrochim. Acta, 18, 433 (1973).
23. F. Fukawa et.al., Bull. Chem. Soc. Jap., 35, 1703 (1962).
24. (a) Y. Izumi et.al., ibid., 44, 1418 (1971). (b) T. Harada et.al., ibid., 44, 1419 (1971). (c) T. Ninomiya, ibid., 45, 2545, 2548, 2551, 2555, (1972). (d) T. Tanabe and Y. Izumi, ibid., 46, 1550 (1973).
25. J. D. Morrison et.al., J. Amer. Chem. Soc., 93, 1301 (1971).
26. P. Bonvicini, Chem. Commun., 1188 (1972).
27. L. Horner and H. Siegel, Phosphorus, 1, 209 (1972).
28. (a) K. Yamamoto et.al., J. Organometal. Chem., 46, 65c, (1972). (b) K. Yamamoto et.al., ibid., 54, 45c (1973).
29. Y. Ohgo et.al., Bull. Chem. Soc. Jap., 44, 583 (1971). (b) Y. Ohgo et.al., ibid., 45, 933 (1972).
30. T. Yoshida and K. Harada, ibid., 44, 1062 (1971).

NEW ANNELATION METHODS AND THEIR APPLICATIONS IN ORGANIC SYNTHESIS

Reported by Alex M. Nadzan October 22, 1973

INTRODUCTION

Annelation reactions are ring forming reactions which often involve fusion of a new ring onto a preexisting one. Such conversions are extremely valuable in organic synthesis especially in the field of natural products where fused ring systems are quite common and often very complex. In natural product synthesis, construction of the correct stereochemistry at centers of ring fusion is essential, thus, annelation reactions must yield products with specific and predictable stereochemistry if they are to be useful.

Structures containing two or more fused six-membered rings are very common in steroids, terpenes and antibiotics, and numerous methods are available for the production of such ring systems. Some of the more general methods include Robinson annelations,[1] Diels-Alder reactions,[2] and intramolecular acylations.[1] More recently, stereospecific biogenetic-like polyene cyclizations have been used to construct fused cyclohexane rings in terpene and steroid intermediates.[3] All of the above methods, however, are best applied or even restricted to six-membered ring formations.

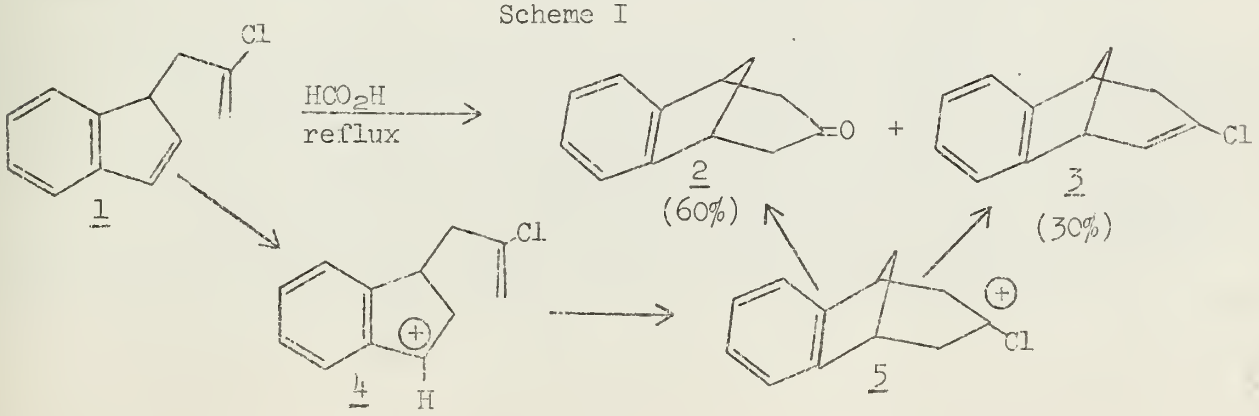
Although fused five and seven-membered rings are found in natural products (steroids, terpenes, hydroazulenes) there are comparatively few direct methods for their synthesis.[4] Quite often, five-membered rings are generated by ring contraction of a cyclohexanone derivative as in the synthesis of normal D ring and A-nor steroids,[5] although direct synthesis of Δ^2-cyclopentenones *via* the aldol condensation of 1,4-dicarbonyl compounds has some generality.[6] Seven-membered rings are often obtained indirectly by ring expansion of cyclohexanones with diazoalkanes.[7] Spiroannelated ring systems are also obtained indirectly from ring closure *via* alkylation reactions or by a combination of alkylation and condensation *via* Diechmann or aldol condensations.[7]

Recently, many novel annelation methods have been developed including intramolecular coupling of allylic α,ω-dihalides with nickel carbonyl,[8] Muxfeldt's bis annelation route to Terramycin,[9] use of heterocyclic isoxazoles for fused-cyclohexanones,[10] and the growing application of photochemical annelation reactions in synthesis of natural products.[11] This seminar will consider some recent and apparently general annelation methods for synthesis of fused cyclopentanones, spirocyclobutanones and spirolactones.

CHLORO OLEFIN ANNELATION

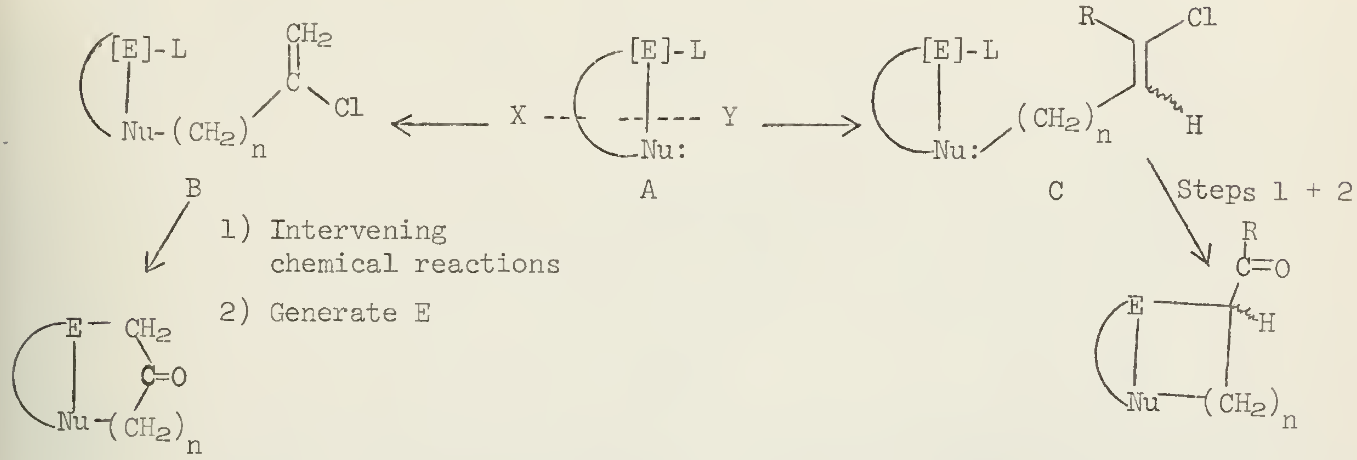
The initial observation by Lansbury[12] that the chloroallyl indene, 1, could be transformed into the benzobicyclic ketone, 2, upon treatment with formic acid, has lead to a general method for synthesis of fused cyclopentanones (Scheme I). The conversion proceeds *via* generation of benzylic carbonium ion 4 which subsequently attacks the vinyl chloride moiety to produce ion 5. Capture of solvent by 5 ultimately leads to carbonyl 2 with a lesser amount of 3 produced from β-elimination. The key step in the conversion is that of ring closure by intramolecular electrophilic attack at the chloro olefin center.

Scheme I

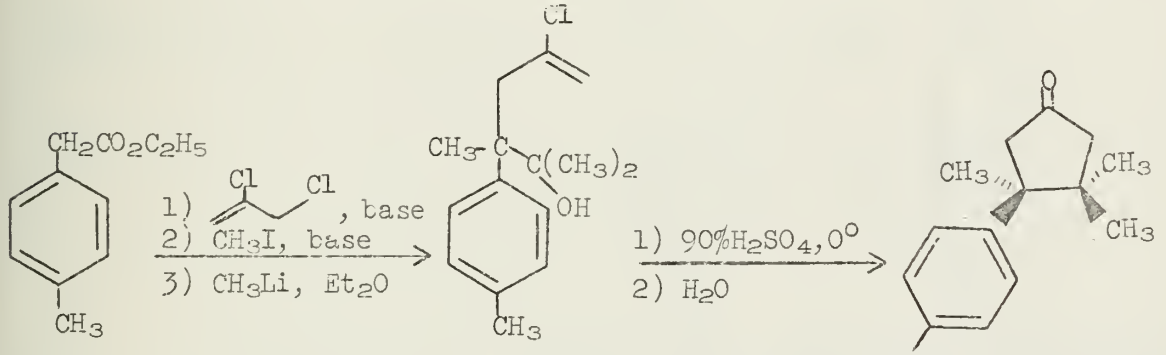


The general annelation method developed (Scheme II) has been successfully applied to synthesis of five, six and seven-membered ring ketones.[13] Formula A represents a potentially bifunctional molecule which either may be cyclic (no dotted lines) or acyclic (cleavage at X orY).

Scheme II



"E" represents a potential electrophilic center and "Nu" corresponds to a nucleophilic center to which the chloro olefin side chain may be attached. It has been established that the "inert" vinyl chloride containing side chain permits intermediate chemical transformations in the molecule prior to the cyclization step, ie., vigorous organometallic addition, lithium aluminum hydride reductions and base induced alkylations. This function also provides thermodynamically controlled stereoselectivity in ring closure to produce a bicyclic ring system as well as permitting the initially generated carbonium ion to rearrange prior to closure especially if a more stable ion results.



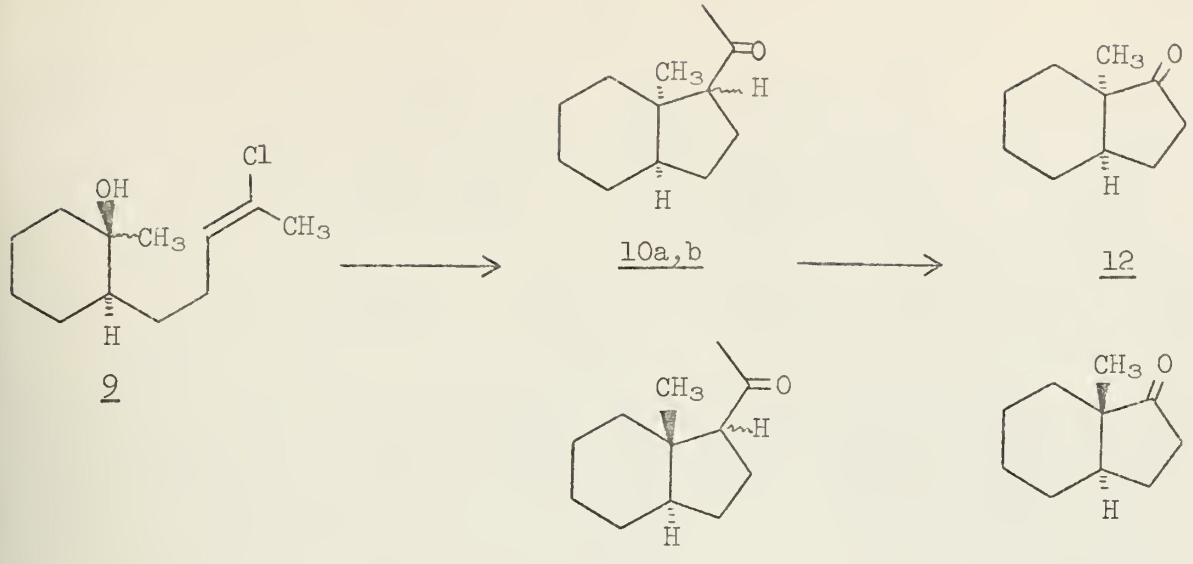
6 7 8

(1)

One of the initial applications of chloro olefin annelation which illustrates this method is the synthesis of sesquiterpene β-cuparenone (8) from 7 (eq. 1).[14]

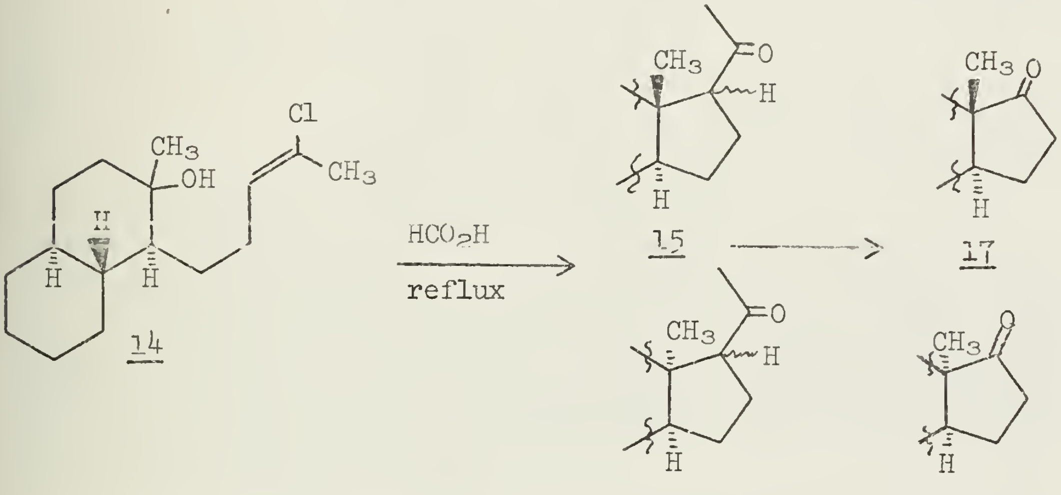
Chloro olefin annelation has been investigated for synthesis of the D ring in 20-keto steroids, a difficult problem in total synthesis.[15] Formolysis of model carbinol 9 produced nearly quantitative yields of four acetyl hydrindans of which the two epimeric cis-fused ketones, 10a,b, were found as major components Degradation of the side chains provided ketones 12 and 13 in a ratio of 3:1.

In an effort to achieve stereoselective formation of the desired trans-fused system, a more conformationally rigid bicyclic system was studied. Formolysis of 14 afforded compounds 15 and 16 in high yield (> 95%). Nmr analysis of the mixture showed the desired trans isomers to be the major products.

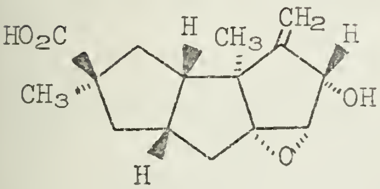


9 10a,b 12 11a,b 13

Degradation of the side chains produced bicyclic ketones 17 and 18 in a ratio of 3:2. Although results were encouraging, subsequent experiments indicated that the desired *trans* stereoselectivity could not be increased above 65%.



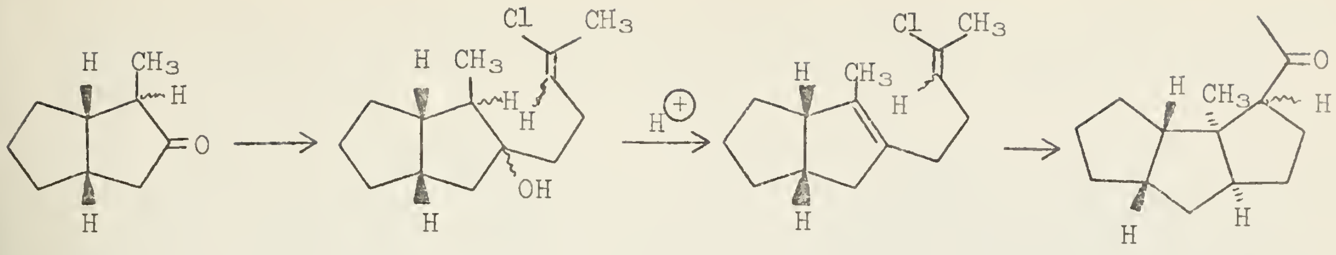
14 15 17 16 18



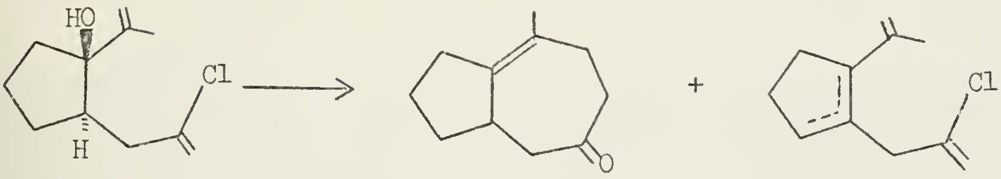
19

Chloro olefin annelation has been successfully employed to generate the tricyclic skeleton of the fungal sequiterpene Hirsutic acid C (19).[16] Model experiments started with either C-2 epimer of 2-methyl-*cis*-bicyclo(3.3.0)octan-3-one, 20, and required addition of Grignard reagent derived from 2-chloro-5-bromo-2-pentene to produce 21 which undergoes formolysis to afford tricyclic ketone 23 as a 4:1 epimeric mixture with the desired *cis*-*anti*-*cis* configuration. The product stereochemistry can be rationalized by the initial dehydration of 21 to yield 22 which then undergoes reversible protonation and closes only when the 2-chloro-2-pentenyl side chain approaches the carbonium ion from the less hindered "convex" face.

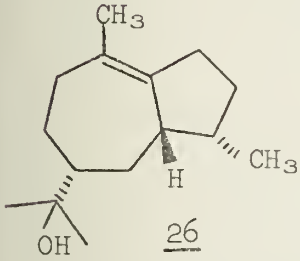
A very recent application of the chloro olefin annelation method is the synthesis of the bicyclic hydroazulenic ring system.[17] Addition of 2-(2-chloroallyl)cyclopentanone to 2-propenylmagnesium bromide provided 24 in ca. 80% yield. Upon treatment with formic acid, 24 gave the hydroazulenone, 25, in 80% yield. Formation of the cycloheptanone in preference to the cyclopentanone is apparently due to the relatively high strain associated with formation



20 21 22 23



24 25



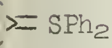
26

of the chloro carbonium ion derived from the latter. This method may become the preferred route for synthesis of hydroazulenic sesquiterpenes such as bulnesol (26) once the problem of stereoselective introduction of the isopropyl side chain in solved.

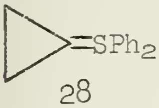
Other potentially useful applications of chloro olefin annelation include the synthesis of certain spiroannelated ring systems,[13] cyclopentyl carboxylic acids,[18] and various heterocyclic ring systems containing sulfur and nitrogen.[13]

SPIROANNELATION WITH CYCLOPROPYL SULFUR YLIDES

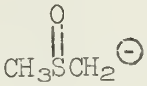
Recent developments in synthesis of cyclopropydiphenylsulfonium fluoroborate and 2-methylcyclopropyldiphenylsulfonium fluoroborate have made ylides 27 and 28 readily available.[19] Both behave as typical sulfur ylides and react with ketones and aldehydes to provide epoxides,[1] however, the epoxides produced from these are highly reactive oxaspiropentanes which may be converted directly or indirectly to cyclobutanones, vinylcyclopropanols, fused cyclopentanones and γ-butyrolactones in high yield.



27



28

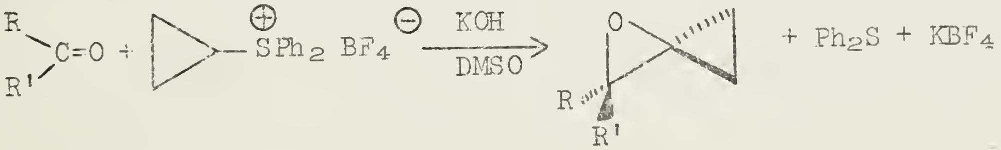


$CH_3\overset{O}{\overset{\|}{S}}CH_2^{\ominus}$

29

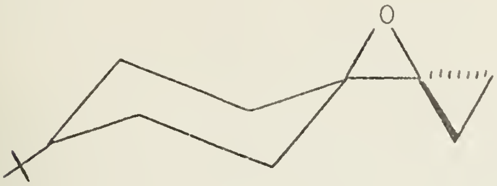
Cyclopropylylides 27 and 28 may be generated from from the fluoroborate salts either irreversibly by treatment with dimsyl anion (29) in dimethoxyethane at -40° or reversibly with powdered potassium hydroxide in dimethyl sulfoxide at 25°.[20] Usually the latter method is preferrable since it is more convenient and generally gives higher yields.

Generation of cyclopropylylides 27 or 28 in the presence of aldehydes or ketones affords oxaspiropentanes (eq. 2).[21] Yields are usually quite high (80-100%) and reaction times are reasonably short. Limitations appear to be poor reactivity with highly hindered ketones, addition to double bonds of conjugated systems to afford spiropentanes instead of oxaspiropentanes, and little or no reaction with ketones which tend to enolize (eg., 6-methoxy-2-tetralone).[22]

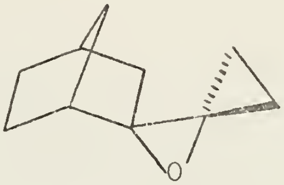


(2)

The reaction is highly stereoselective as indicated by formation of single oxaspiropentanes 30 and 31 from 4-*t*-butylcyclohexanone and norcamphor respectively. In both cases attack occurs from the less hindered side (equatorial and exo attack respectively).

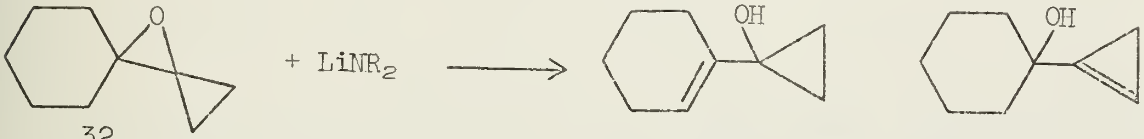


30



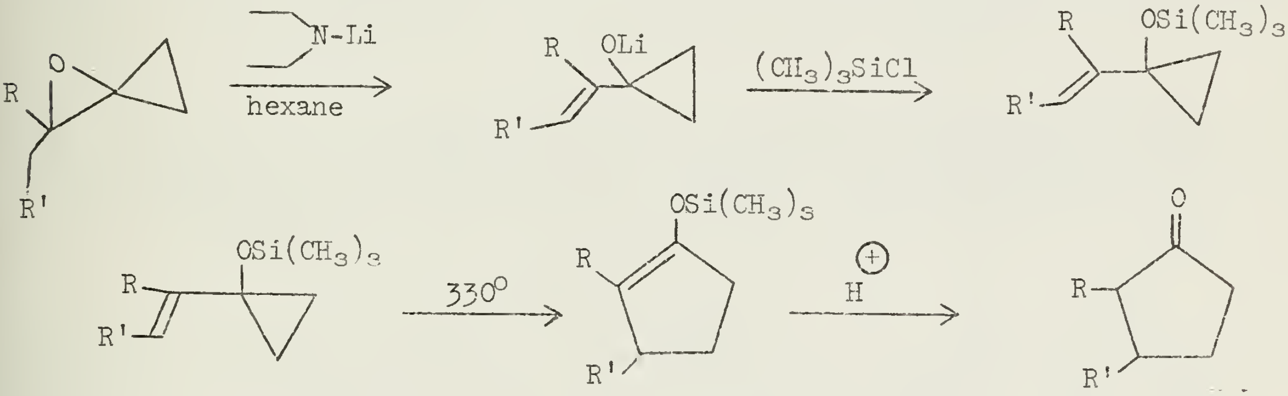
31

Oxaspiropentanes behave as highly reactive epoxides and undergo base-induced elimination to allyl alcohols.[22] The reaction employs a lithium dialkylamide and exhibits unusually high orientational and stereochemical requirements; preference for elimination is primary>>secondary>>tertiary. Extension of this reaction to oxaspiropentane 32 afforded vinylcyclopropanol 33 and the monoalkylcyclopropene 34. The ratio of products obtained was highly dependent on solvent and base employed; lithium diethylamide in pentane gave a high yield of the desired vinylcyclopropanol (33:34 = 9:1).



32 33 34

It is known that vinylcyclopropanols rearrange thermally to cyclobutanones and undergo ring expansion with a variety of electrophilic reagents to form substituted cyclobutanones.[23] Recently, trimethylsilyl ethers of vinylcyclopropanols have been observed to thermally rearrange to enol silyl ethers which, upon hydrolysis, afford cyclopentanones.[22] Treatment of oxaspiropentanes with lithium diethylamide in hexane and work-up of the reaction in the presence of trimethylchlorosilane results in siloxyvinylcyclopropanes which are purifiable by distillation or column chromatography (eq 3).



(3)

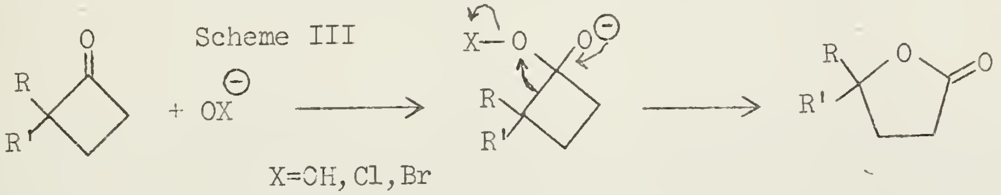
(4)

Passage of hexane solution of the silyl ether over a column of glass helices at 330° with contact time of four seconds affords rearranged enol silyl ethers (eq. 4). Brief treatment with acid provides high yields of cyclopentanones. Although multiple steps are involved, yields in each step are excellent (89-99%). It is also of interest to note that the rearranged enol silyl ether may be alkylated by conversion to the lithium enolate with subsequent addition of alkylating agent via the method of Stork[24] and House.[25] The overall process is, thus, a useful method for conversion of carbonyl compounds to cyclopentanones.

Another very useful reaction of oxaspiropentanes is their facile, acid promoted rearrangement to cyclobutanones.[26] As in previous conversions, the yields are excellent and the cyclobutanones can be obtained simply by work-up of the oxaspiropentane with aqueous fluoroboric acid. With cyclic ketones, the reaction is highly stereoselective; isomer distribution is dependent on the Lewis acid catalyst employed.

Cyclobutanones, because of their high strain energy (~27 kcal/mole), permit facile Baeyer-Villiger oxidations with peroxide derivatives normally incapable of effecting such transformations.[27] Thus, peroxide oxidation of spirocyclobutanones allows smooth conversion to γ-butyrolactones in isolated overall yields of 57-92%, based upon starting ketone or aldehyde. The rearrangements which utilize hypochlorous acid, basic hydrogen peroxide or sodium hypobromite, are completely analogous to the peracid catalyzed Baeyer-Villiger process.[28] The order of migratory perference appears to be tertiary>secondary>primary and migration occurs with retention of configuration at the migrating carbon (Scheme III). The use of basic hydrogen peroxide as the rearranging reagent permits the presence of double bonds which would interfere with normal peracid methods.

Scheme III



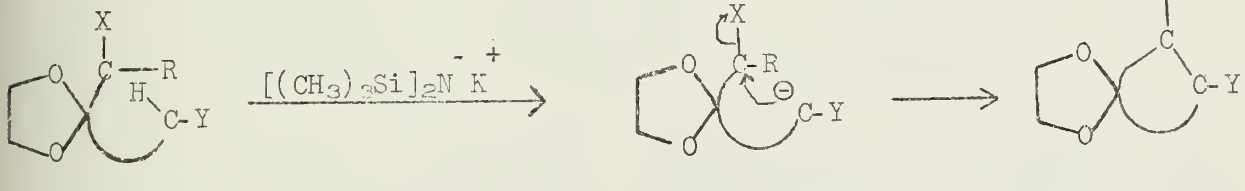
The above conversion, termed "lactone annelation," appears to be the method of choice when compared to previous methods employed for generation of such spirolactones.[26] The transformation of γ-butyrolactones to cyclopentenones also increases the potential utility of this method.[29]

The general utility of cyclobutanones has been expanded, recently, by the ability to form cyclobutanones from conjugated carbonyl systems. As mentioned previously, addition of cyclopropylides 27 and 28 to conjugated system affords spiropentanes instead of oxaspiropentanes or cyclobutanones.[30] However, reaction of 1-lithiocyclopropyl phenyl sulfide with highly hindered and/or conjugated systems affords cyclobutanones in moderate to high yield after mild acid hydrolysis.[31] Such conversions greatly expand the potential use of the spiroannelation and lactone annelation in synthesis.

HALOKETAL CYCLIZATION

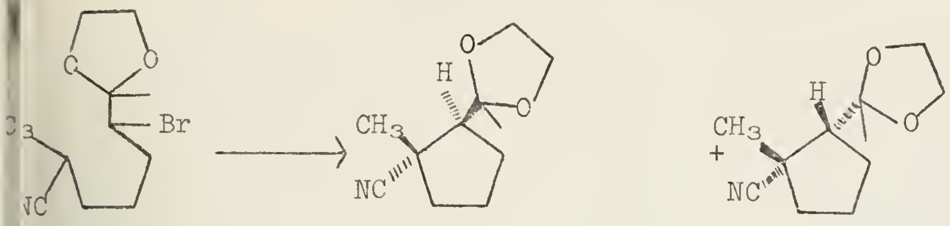
An extremely valuable cyclization reaction has been studied by Stork and coworkers.[32] They demonstrated that substituted haloketals cyclize stereoselectively upon treatment with potassium hexamethyldisilazane in benzene (Scheme IV). The reaction is conducted either at room temperature

Scheme IV

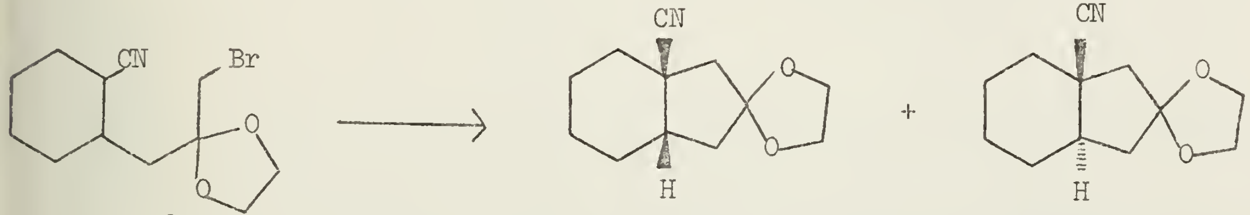


for 8-20 hr or at reflux for 1-4 hr, however, the former is preferrable since higher yields and greater stereoselectivity is obtained. The reaction may be carried out on α-chloro- as well as α-bromoketals although the former react somewhat more slowly. Yields for all reaction studies (Y=CN or CO_2Et) were high, 70-85% of distilled or recrystallized product.

Monocyclic and fused five-membered systems may be synthesized as illustrated below (eq. 5 and 6). Cyclization of 35 provides 36 and 37 (92:8); it is of potential synthetic utility that the isomer formed (36) is the less stable one as indicated by the fact that hydrolysis of the ketal and reketalization



35 36 37 (5)



38 39 40 (6)

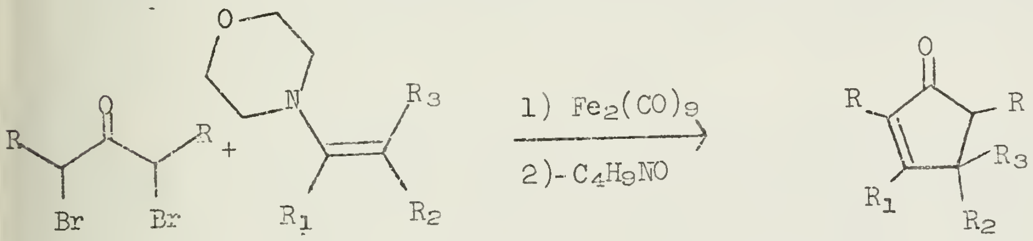
leads to isomer 37 (36:37=3:97). Cyclization of 38 affords hydrindans 39 and 40 (94% yield) with the *cis* fused product as the major component (39:40=89:11).

Variation of halogen or metal ion has little effect on the stereochemical outcome for five-membered ring formation but profoundly alters the outcome in cyclizations to six-membered rings.[33] *Cis*-decalin systems are obtained with potassium hexamethyldisilazane while *trans* isomers result from treatment with the lithium base.

The high yields and stereoselectivity of this reaction along with the presence of ketal and cyano or ester functions in the products should be most useful for synthesis of complex molecules.

CYCLOPENTENONES FROM DIBROMO KETONES AND ENAMINES

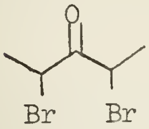
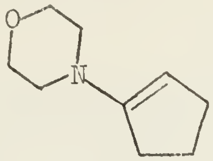
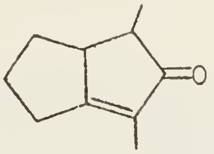
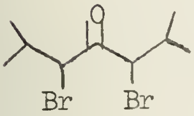
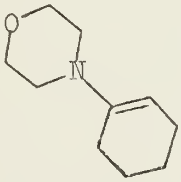
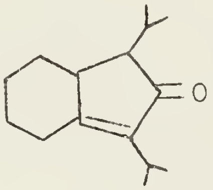
Intermolecular coupling of α,α'-dibromo ketones and morpholine enamines in the presence of iron carbonyls has lead to a novel cyclopentenone synthesis (eq. 7).[34] The reaction is conducted in dry benzene at 25-30° for 12 hr under nitrogen and usually provides good yields of both fused and monocyclic cyclopentenones (Table I). Iron pentacarbonyl may be used but it is less effective. An important limitation of the reaction is that dibromides derived from acetone and other methyl ketones afforded little if any cyclic adducts.



(7)

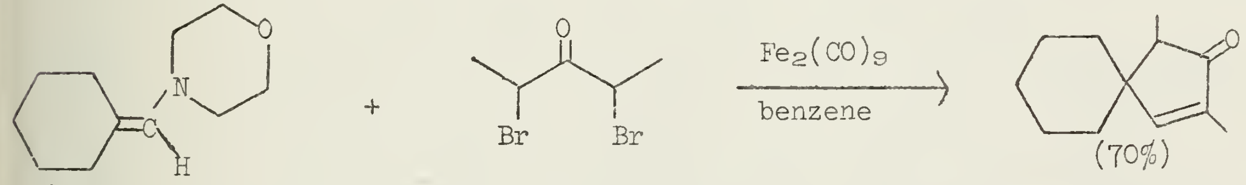
It is also important to note that dibromo ketones with no hydrogen atoms α to the carbonyl group give rise to stable β-morpholino ketones and, under the above reaction conditions, α,α'-dibromo ketones may react with dienes to afford cycloheptenones.[35]

Table I. Iron Carbonyl Promoted Cyclopentenone Synthesis.*

Dibromide	Enamine	Product	Yield, %
			75
			77

*Reaction was performed in dry benzene at 25° for 12 hr using α,α'-dibromo ketone, enamine, and $Fe_2(CO)_9$ in a mole ratio of 1.0:2.5-3:1.2.

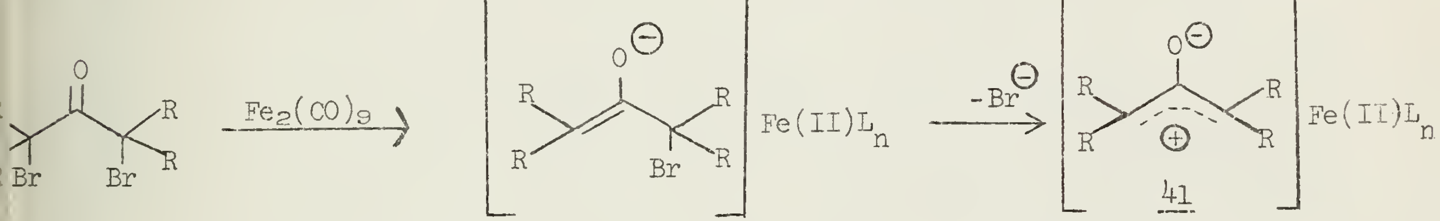
Spiro compounds may also be produced by reduction of α,α'-dibromo ketones in presence of enamines derived from cycloalkanecarboxaldehydes (eq. 8).



(8)

Mechanistic studies of this reaction and related ones implicate an oxyallyl-iron(II) intermediate, 41, (L = $Br^{\ominus}$, CO, solvent, etc.) as outlined in Scheme V.[36]

Scheme V



Although the method does not afford unsubstituted cyclopentenones, it does produce α,α'-dialkylcyclopentenones directly thus avoiding the tedius, multistep techniques which are required to α-alkylate cyclic ketones, particularly with bulky alkyl groups.[37]

CONCLUSIONS

The new annelation methods discussed offer the synthetic chemist alternatives to existing methods for construction of simple and complex molecules. Application of these methods will obviously be dictated by the specific synthetic problem at hand, since each method has certain limitations. Chloro olefin annelations cannot be applied to synthesis of molecules which tend to undergo undesirable skeletal rearrangements or functional group modifications in highly acidic medium. In addition, the thermodynamic stereochemical control of product composition may not afford the intermediate or product of interest. Correspondingly, spiroannelation reactions with cyclopropyl sulfur ylides are not successful for aldehyde or ketone groups which tend to enolize or are extremely hindered. Haloketal cyclizations to fused five-membered rings afford only the cis isomer and the reaction of α,α'-dibromo ketones with enamines is unsuitable for synthesis of unsubstituted cyclopentenones.

In terms of general utility, however, spiroannelation via cyclopropyl sulfur ylides appears to offer much potential. The ready availability of oxaspiropentanes, substituted cyclobutanones and γ-butyrolactones should initiate future research into new reactions of these highly interesting molecules.

BIBLIOGRAPHY

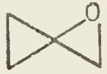
1. H. O. House, "Modern Synthetic Reaction," 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, Chapters 9-11.
2. W. A. Carruthers, "Some Modern Methods of Organic Synthesis," Cambridge University Press, London, 1971, Chapters 1, 3 and 5.
3. W. S. Johnson, Accounts Chem. Res., 1, 1 (1968).
4. P. T. Lansbury, E. J. Nienhouse, D. J. Sharf and F. R. Hilfiker, J. Amer. Chem. Soc., 92, 5649 (1970).
5. C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, Chapter 11.
6. A. T. Nielsen and W. J. Houliken, Org. React., 16, 1 (1968).
7. J. B. Jones and P. Price, Chem. Commun., 1478 (1969).
8. E. J. Corey and E. Hamanaka, J. Amer. Chem. Soc., 89, 2758 (1967); E. J. Corey and H. A. Kirst, ibid., 94, 667 (1970).
9. H. Muxfeldt, G. Hardtmann, F. Kathowala, E. Vedejs and J. B. Mooberry, ibid., 90, 6534 (1968).
10. G. Stork, S. Danishefsky and M. Ohashi, ibid., 89, 5459 (1967); G. Stork and J. E. McMurray, ibid., 89, 5461, 5463, 5464 (1967).
11. P. G. Sammes, Quart. Rev., Chem. Soc., 24, 37 (1970).
12. P. T. Lansbury and E. J. Nienhouse, J. Amer. Chem. Soc., 88, 4290 (1966); P. T. Lansbury and E. J. Nienhouse, Chem. Commun., 1007 (1967).
13. P. T. Lansbury, Accounts Chem. Res., 5, 311 (1972).
14. P. T. Lansbury and F. R. Hilfiker, Chem. Commun., 619 (1969).
15. P. T. Lansbury and G. E. Dubois, ibid., 1107 (1971).
16. P. T. Lansbury and N. Nazarenko, Tetrahedron Lett., 1833 (1971).
17. P. T. Lansbury, P. M. Wovkulick, P. E. Gallagher; ibid., 65 (1973).
18. P. T. Lansbury and R. C. Stewart, ibid., 1569 (1973).
19. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5298 (1973).
20. B. M. Trost and M. J. Bogdanowicz, ibid., 93, 3773 (1971).
21. B. M. Trost and M. J. Bogdanowicz, Tetrahedron Lett., 887 (1972).
22. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5311 (1973).
23. H. H. Wasserman, R. E. Cochoy and M. S. Baird, ibid., 91, 2375 (1969); H. H. Wasserman, H. W. Adickes, and O. Espejo de Ochoa, ibid., 93, 5586 (1971); J. R. Salaun and J. M. Conica, Tetrahedron Lett., 2849 (1972).
24. G. Stork and P. F. Hudrlik, J. Amer. Chem. Soc., 90, 4462, 4464 (1968).
25. H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, J. Org. Chem., 34, 2324 (1969); H. O. House, M. Gall, and H. D. Olmstead, ibid., 36, 2361 (1971).
26. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem Soc., 95, 5321 (1973).
27. B. M. Trost and M. J. Bogdanowicz, Tetrahedron Lett., 923 (1973).
28. H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 6.
29. P. W. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, J. Org. Chem., 37, 1947 (1972).
30. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5307 (1973).
31. B. M. Trost, D. Keeley and M. J. Bogdanowicz, ibid., 95, 3068 (1973).
32. G. Stork, J. O. Gardner, R. K. Boeckman, Jr. and K. A. Parker, ibid., 95 2014 (1973).
33. G. Stork and R. K. Boeckman, Jr., ibid., 95, 2017 (1973).
34. R. Noyori, K. Yokoyama, S. Makino and Y. Hayakawa, ibid., 94, 1772 (1972).
35. R. Noyori, S. Makino and H. Takaya, ibid., 93, 1272 (1971).
36. R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi and S. Tsutsumi, ibid., 94, 7202 (1972).
37. For a method of synthesis of α,α-dialkylcyclopentanones, see R. M. Coates and R. L. Soweby, ibid., 93, 1027 (1971), and references cited therein.

OXASPIROPENTANES: FORMATION AND USE AS SYNTHETIC INTERMEDIATES

Reported by Richard L. Neeley October 25, 1973

SCOPE

Oxaspiropentane (1) and its derivatives are highly strained ring systems which undergo ring openings under mild conditions which can be selectively varied to afford several different products. The first oxaspiropentane was synthesized in 1967 as a model for strained epoxide ring systems.[1] Other derivatives have since been synthesized,[2-4] but until recently were not evaluated as synthetic intermediates, in part due to inefficient preparative methods. Recently, Trost and Bogdanowicz[5] have introduced a two-step sulfonium ylide method which affords oxaspiropentanes in high yields. This review examines the formation of oxaspiropentanes and their possible use as intermediates in the formation of several synthetically important systems.

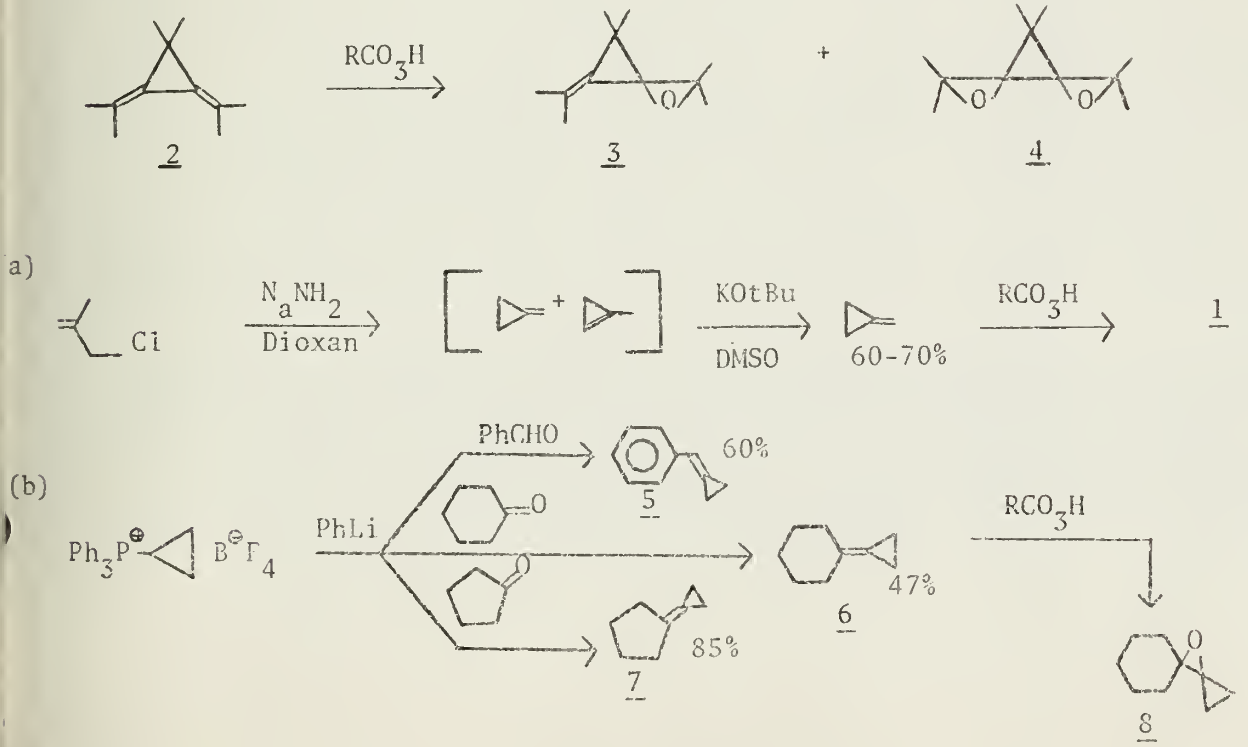


1

METHODS OF PREPARATION

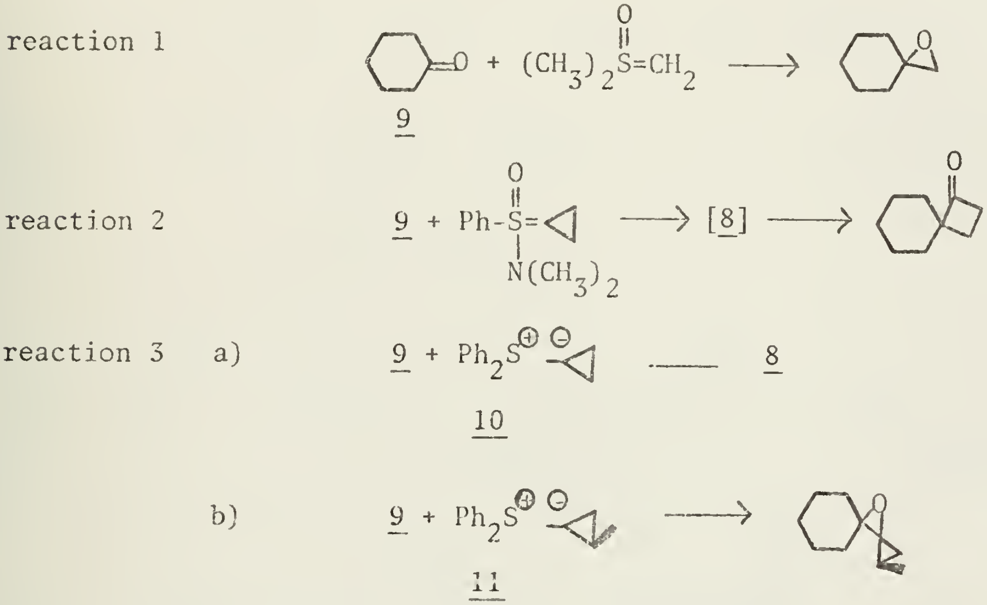
Early workers, being interested in model epoxides, approached the problem of synthesis by preparing methylenecyclopropane derivatives from which they obtained the oxaspiropentanes by epoxidation. Such epoxidations are generally quantitative,[6] overall yields being limited by availability of the methylenecyclopropane intermediates. Crandall and Paulson[1] prepared the first oxaspiropentanes, 3 and 4, by peracid epoxidation of the dimethylenecyclopropane 2 obtained by a series of pyrolyses from an allene precursor (Scheme I). Feasibility of this method of synthesis lies in a systematic approach to formation of the methylenecyclopropane intermediates. Two general approaches are possible: (a) closure of the cyclopropane ring in a system already containing a double bond, or (b) formation of a double bond exo to a cyclopropane ring. Method (a) was used by earlier workers and several preparative methods were developed.[7] At present, highest yields are obtained by the reactions shown in Scheme I, pathway (a).[8] This is similar to the method used by Salaun and Conia[2] to produce the parent compound (1) in 60% yield. Method (b) is easily accomplished by a Wittig reaction. Schwitzer[9] synthesized the methylene cyclopropane derivatives 5-7 using a cyclopropyltriphenylphosphonium ylide. This is the same method used by Wiseman and Chan[3] to produce the oxaspiropentane 8 in 46% yield after epoxidation.

Scheme I



More recently, attempts have been made to prepare oxaspiropentanes directly by the action of sulfur ylides on carbonyl compounds, analogous to known reactions of methylides to form epoxides (Scheme II).[10] Johnson et al.,[4] using N,N-dimethylaminophenyloxosulfonium cyclopropylide, have proposed the oxaspiropentane 8 as an intermediate in reaction 2, but have been unable to isolate it. Most recently, Trost and Bogdanowicz, using a series of new sulfonium ylides,[10] have produced oxaspiropentanes in yields of 80-100% from ketones and aldehydes (reaction 3). This method appears likely to replace previous methods of preparation as it affords cleaner products in higher yields than former methods.

Scheme II

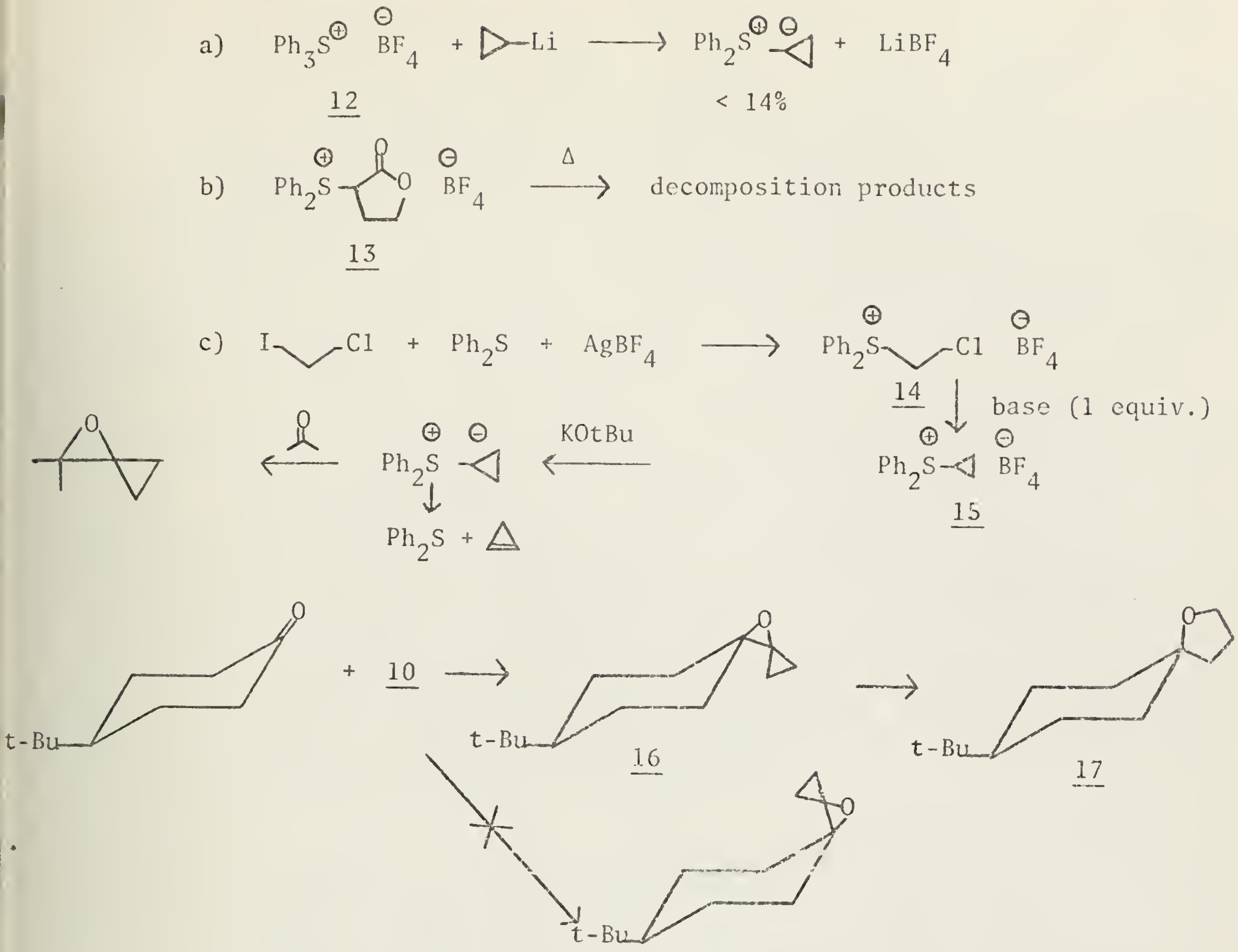


FORMATION AND REACTION OF YLIDES

Several methods have been used to produce the cyclopropylides needed for oxaspiropentane synthesis. Ligand exchange methods using triphenylsulfonium fluoroborate, 12, and cyclopropyllithium were initially used but work poorly (14% yield).[12] Attempts to use sulfonium salt 13, analogous to a high yield preparative method for forming cyclopropylphosphonium ylides, were unsuccessful in producing preparative yields. At present, cyclopropylsulfonium ylides have been produced in highest yield by the method given in Scheme III (c).[11] The nucleophilic attack of diphenyl sulfide on a 1,3-dihalopropane in the presence of silver tetrafluoroborate leads to the sulfonium salt 14. Ring closure by base affords diphenylcyclopropylsulfonium fluoroborate, 15. When isolation of the reactant is desired, it is generally isolated as the fluoroborate salt since diphenylsulfonium cyclopropylide has a half-life of about $2\frac{1}{2}$ minutes at 25°. Generation of the ylide is accomplished by base in the presence of the carbonyl group to which addition is desired. In this manner, few decomposition products are found as attack of the ylide at carbonyl centers is more rapid than decomposition.

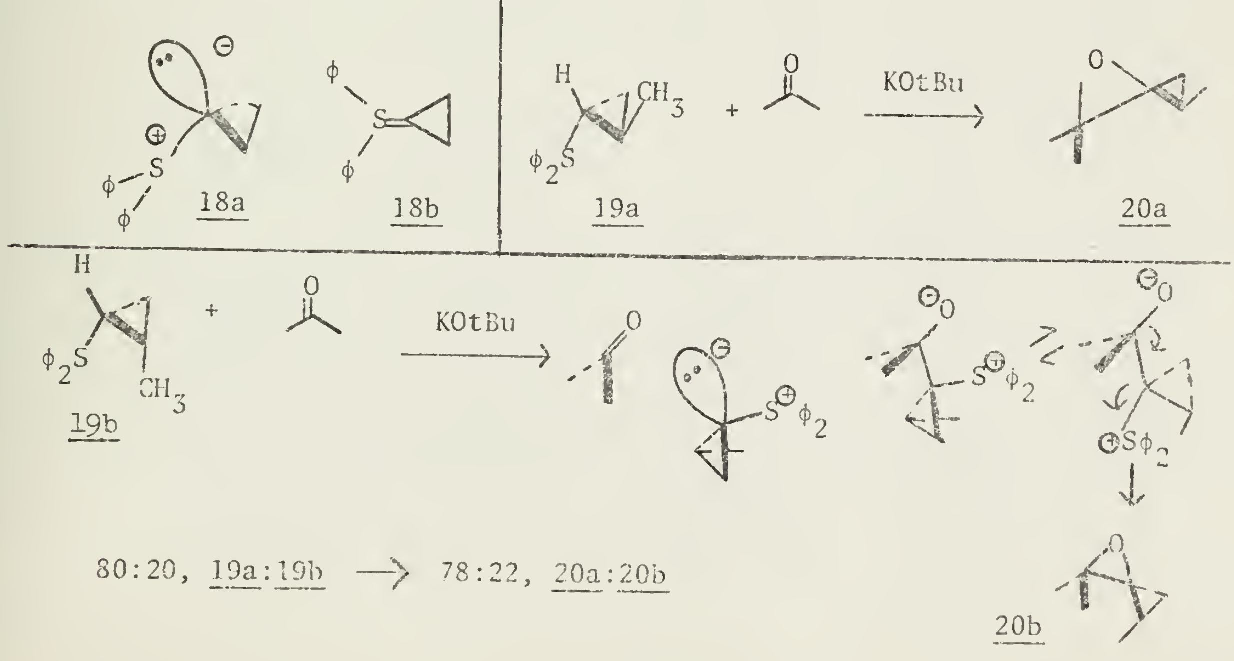
Attack of ylide 10 at carbonyl centers in rigid systems has been shown to be highly stereoselective. Reaction with 4-t-butylcyclohexanone gave a crystalline solid, 16, with a sharp melting point (26.5-27°), indicating a single diastereomer.[5] As additional proof, 16 was converted to the tetrahydrofuran 17 which was also available by an independent synthesis. Both samples of 17 were identical by vpc.[13] These results are compatable with previous studies which indicate that attack of sulfur ylides on rigid six membered cyclic ketones is equatorial.[14]

Scheme III


a) Ph3S⊕ ⊖BF4 + ▷—Li → Ph2S⊕⊖◁ + LiBF4
12
< 14%
b) Ph2S⊕ ⊖BF4 Δ → decomposition products
13
c) I—Cl + Ph2S + AgBF4 → Ph2S⊕—Cl ⊖BF4
14
base (1 equiv.)
Ph2S⊕—◁ ⊖BF4
15
KOtBu
Ph2S⊕⊖◁
Ph2S + △
t-Bu
+ 10
16
17

Present data is in agreement with attack of ylide 10 with tetrahedral character at the carbon α to sulfur (18a).[13] Species of the form 18b, which have been shown to be present in phosphonium ylides,[15] are incompatable with present data for sulfonium cyclopropylides. Studies carried out on cis and

Scheme IV

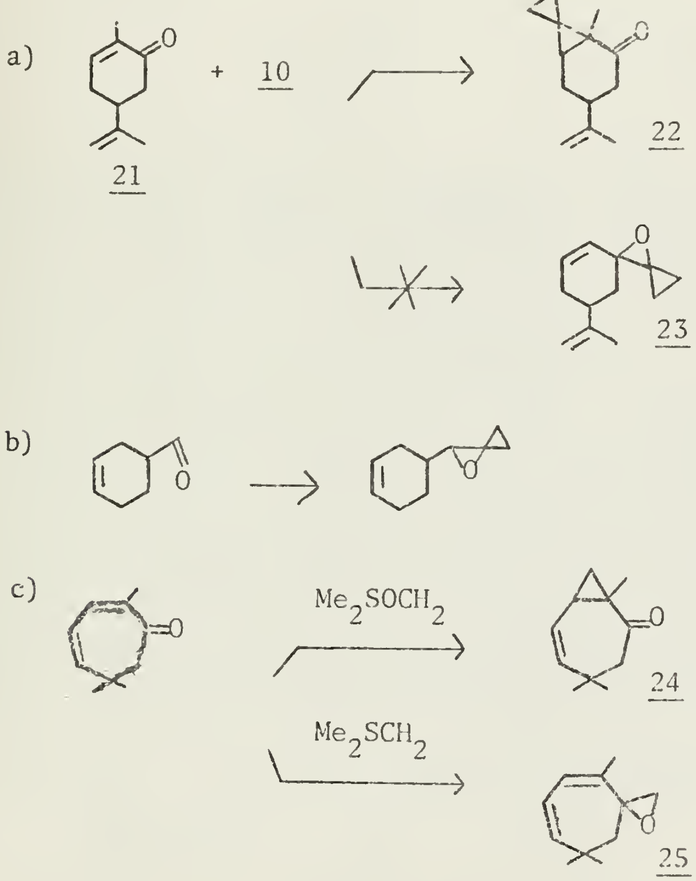


trans 2-methylcyclopropyldiphenylsulfonium fluoroborate and the corresponding ylides, 19a and 19b, indicate that stereochemistry of the tetrahedral α-carbon is retained in initial ylide attack.[11] A mixture of 80:20, 19a:19b gave a 78:22 mixture of 20a:20b as product (Scheme IV). Reactive intermediates similar to 18b would not be expected to show this configuration retention. Inversion of configuration at carbon then takes place by attack of the oxygen of the betaine to displace diphenylsulfide.[16] The slight change in cis/trans product ratio is apparently due to some inversion at the tetrahedral anion center, a process much slower than attack of the ylide on carbonyl centers. It might be expected that steric effects which slow ylide attack would give reduced stereoselectivity but no studies have as yet been undertaken on cyclopropane ring substituents larger than methyl.

DIFFICULTIES IN THE USE OF SULFONIUM CYCLOPROPYLIDES

Although sulfonium ylides appear to be the best choice for most oxispiropentane syntheses, side reactions occur with α,β-unsaturated carbonyl system. Carvone, 21, reacts with ylide 10 to give the spiropentane 22 in 75% yield. No oxaspiropentane 23 can be detected in the reaction.[17] This is a general reaction of sulfur ylides with α,β-unsaturated carbonyls and can be used to produce substituted spiropentanes in high yield. However, if a carbonyl center and a carbon-carbon double bond are present in the same compound but are not conjugated, addition takes place to give the oxaspiropentane exclusively (Scheme V, b). Methylenesulfonium and sulfoxonium ylides have been found which react selectively in conjugated systems to give either epoxides or cyclopropanes. Tany and Rapoport[18] have produced both 24 and 25 from eucarvone by appropriate choice of ylides and reaction conditions (Scheme V, c), but no satisfactory system has yet been developed for cyclopropylides.

Scheme V

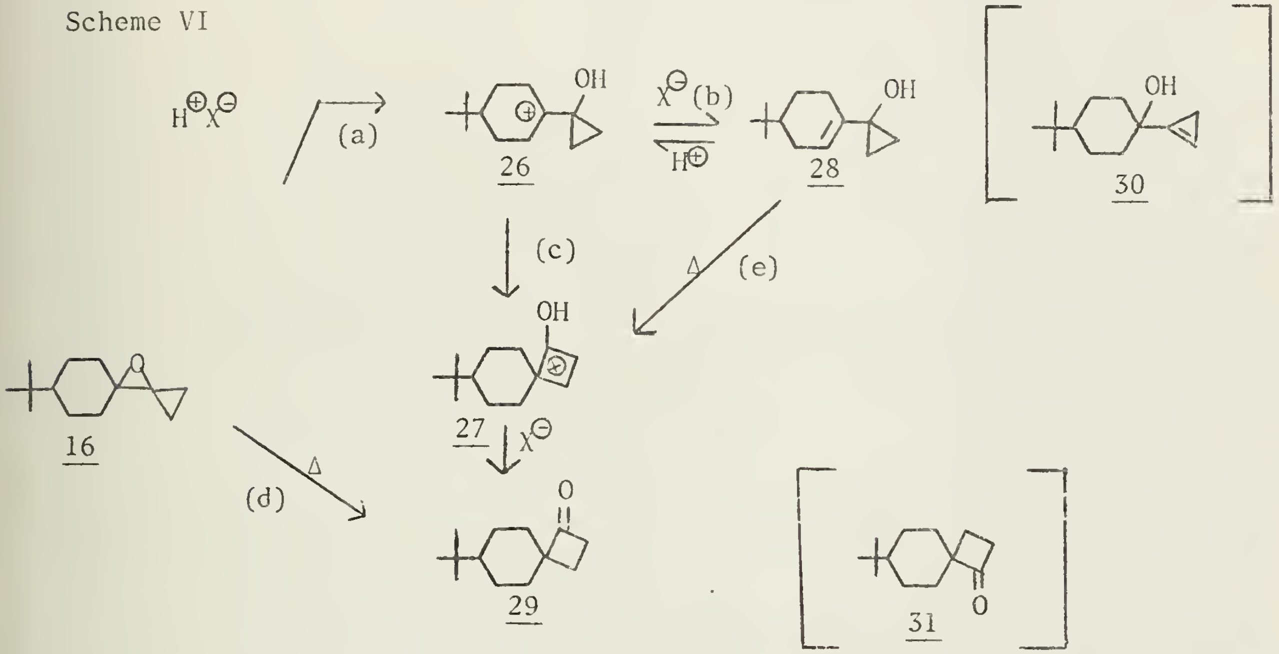


Some difficulty also occurs with sulfonium ylides and hindered carbonyls. Most reactions with these ylides were completed in two hours with yields of greater than 80%. Diisopropylketone reacted slowly and after 24 hours, only 59% of the corresponding oxaspiropentane had been formed. Carbonyls which are more hindered have not been studied, but some lowering of yield (or increase in reaction time) is to be expected. General availability of carbonyl precursors, however, tends to favor sulfur ylides as the method of choice in oxaspiropentane synthesis.

REACTIONS

Use of neutral or basic solutions during the formation of oxaspiropentanes allows them to be isolated. Owing to ring strain energies on the order of 63 kcal./mole,[19] ring openings occur under a variety of acidic and thermal conditions. Two initial products are possible, vinyl alcohols and cyclobutanones.

Scheme VI



Acid treatment(Scheme VI) can produce either vinylcyclopropanols (28) or cyclobutanones (29). The ratio 28/29 is governed by the nature of the acid counterion.[11] Nucleophilic anions, such as halides, tend to abstract protons from intermediate 26 (path b) before bond migration can occur to give the four-membered ring (path c). Non-nucleophilic anions, such as perchlorate, favor path c. Thus the ratio of 28/29 increases in the following order of acid tested: $LiClO_4$, LiBr, HBF_4, HI, HCl.

It is also possible to vary the ratio of cyclobutanone 29 and its isomer, 31, by varying the acid used.[13] Since rotation about the single bond connecting the two ring systems in intermediate 26 is possible, bond shifts which occur before rotation would give 29, while bond shifts occurring after rotation would give 31. Complexation with bulky Lewis acids, such as Eu(fod),[20] give hindered rotation and thus a higher 29/31 ratio. In addition, europium and lithium form more ionic bonds with oxygen than does hydrogen available from protic acids. The increased partial ionic charge on oxygen favors bond migration to the more stable intermediate 27. These results are shown in Table I.

Table I.[13] Reactions of 16 with Lewis Acids

Lewis Acid	29	31
H^+	82	18
Li^+	91	9
Ea^{3+}	99^+	<<1

Two additional pathways, (d) and (e), shown in Scheme VI are thermal and are believed to be concerted. Salaun and Conia[2,21] have shown these concerted pathways to be compatable with molecular orbital symmetry. However, these pathways have been studied less than the ionic pathways and should not be considered proven.[22]

PREPARATION OF CYCLOPENTANONES AND α-SUBSTITUTED CYCLOBUTANONES

A property of oxaspiropentane ring openings common to epoxide reactions is that two possible vinyl alcohols can be formed, 26 or 28, depending on which of the adjacent hydrogens is abstracted.[23] Either 26 or 28 can be obtained as the major product by a proper choice of solvent and base. To prevent reaction by path (c) of Scheme VI to give cyclobutanones, lithium dialkylamides are used. The strongly basic counterion favors hydrogen abstraction over bond rotation and vinyl alcohols are formed with only slight contamination by cyclobutanones. Reactions of epoxide systems with lithium reagents are well known, and are stereoselective. Preference for hydrogen abstraction in elimination is primary>> secondary>> tertiary. When α-hydrogens are on equally substituted carbons, abstraction preference is for syn diaxial elimination.[24] A cyclic intermediate has been proposed. (Scheme VII). Oxaspiropentanes which are formed from acyclic compounds will form 1-vinylcyclopropanols (acyclic analogs of 26) rather than forming the unstable cyclopropene derivatives since free rotation of the carbon bearing the α-hydrogens derived from the former ketone always allows those hydrogens to assume a syn diaxial relationship with the oxygen of the epoxide ring. Oxaspiropentanes formed from cyclic ketones, such as cyclohexanones, can populate two (or more) conformers, such as 32a and 32b. If the transition energy barrier between the two conformers is high due to substituents which raise the energy of one conformer with respect to the other, the conformer interconversions become slower than ring opening and product predictions can be made. In ether, solvent competes with the oxaspiropentane for complexation with the lithium salt leaving the oxaspiropentane largely uncomplexed. Thus equilibrium favors conformer 32a. In non-polar solvents such as pentane, lithium dialkylamides form a tight complex with the oxygen atom of the epoxide ring, favoring conformer 32b. Preference for syn diaxial hydrogen abstraction causes conformer 32a to give the cyclopropene 30 even though ring strain is unfavorable. Conformer 32b leads to abstraction from the six-membered ring to give the more stable cyclohexene 28.

Scheme VII

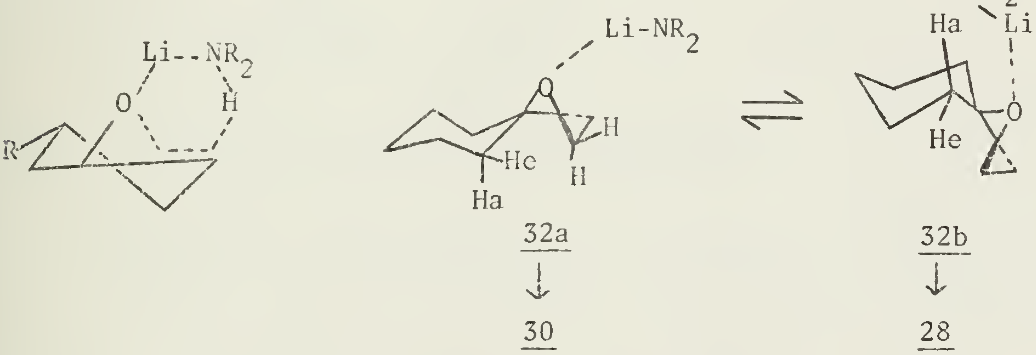
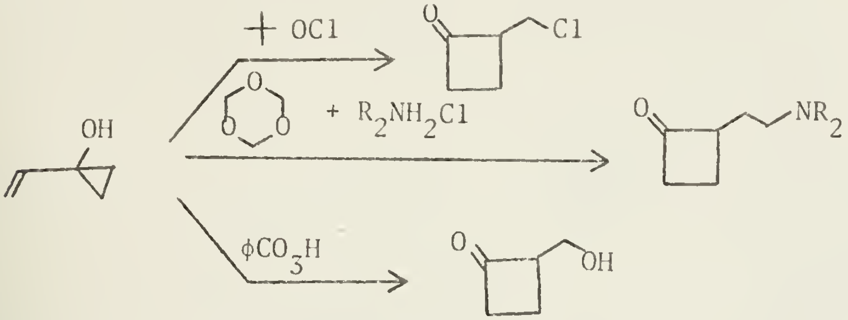


Table II. Reactions of 8 with Lithium Reagents and Solvents

Base	Solvent	28 : 30
Me_2NLi	Ether	1 : 6.25
$i\text{-}Pr_2NLi$	Ether	1 : 7.60
Et_2NLi	Pentane	9.00 : 1

Compound 28 as well as other vinylcyclopropanols have been isolated but are generally subjected to further reaction without isolation. As was seen in reaction scheme VI, ring enlargements to cyclobutanones occur ether thermally or in the presence of acid. Rearrangements also occur in the presence of electrophiles to give substituted cyclobutanones with functionality added α to the cyclobutane ring.[25]



Another series of reactions is made possible by masking the hydroxyl group. The remaining vinylcyclopropane entity has been shown to rearrange thermally to a cyclopentene.[26] Removal of the masking group then leads to a cyclopentanone. This reaction has been carried out using trimethylsilyl ethers formed by the reaction of trimethylsilyl chloride with the lithium salts of the vinylcyclopropanol (Scheme VIII). Base reacts with the siloxyvinylcyclopropane 33 to give an α, β-unsaturated ketone (34). Acid gives the cyclobutanone 35. Pyrolysis at 460° gives a cyclopentene-1-silyl ether 36 which is easily hydrolyzed to give cyclopentanone 37. Double bond formation in intermediates occurs on the least substituted carbon. Thus, 2-octanone gives only terminal double bond formation as can be seen in Table III. None of the isomer with a double bond in the 2-position could be found in the reaction mixture.

Scheme VIII

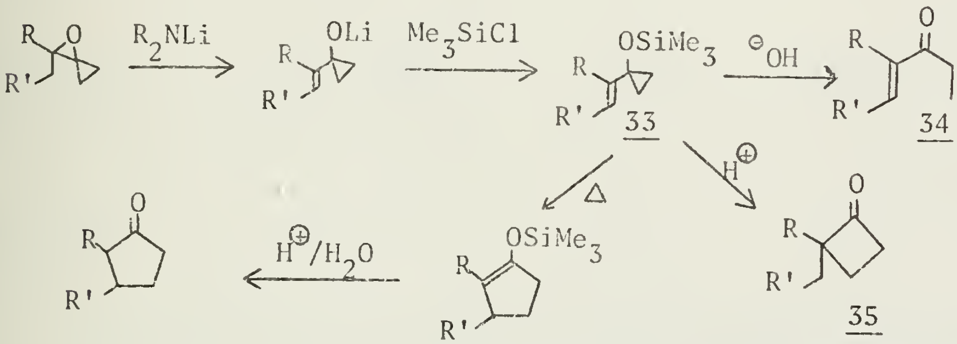
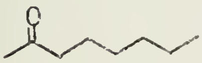
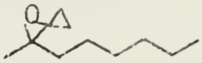
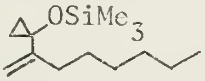
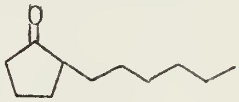
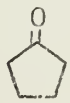
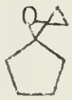
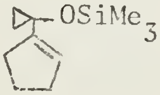
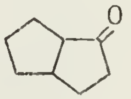
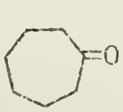
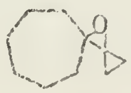
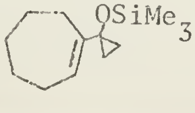
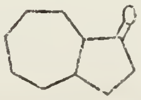


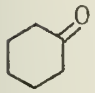
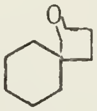
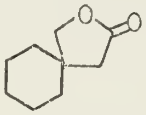
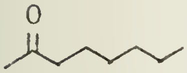
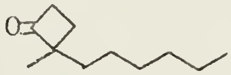
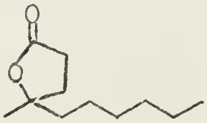
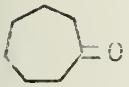
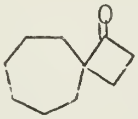
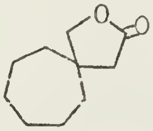
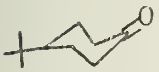
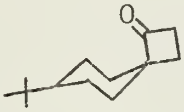
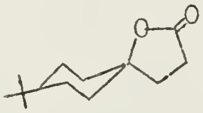
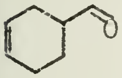
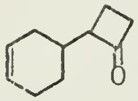
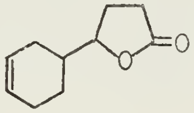
Table III. Formation of Cyclopentanones

Ketone	Oxaspiropentane	Siloxyether	Cyclopentanone	% Overall Yield
				83%
				79%
				72%

PREPARATION OF LACTONES AND CYCLOPENTENONES

Several products of additional reaction are available from the cyclobutanones formed by oxaspiropentane ring opening. Cyclobutanones are available in high yield by refluxing with lithium perchlorate in benzene. Cyclobutanones undergo oxidation to γ-lactones by the Baeyer-Villager reaction under very mild conditions.[27] Several γ-lactones have been synthesized in this manner (Table IV).

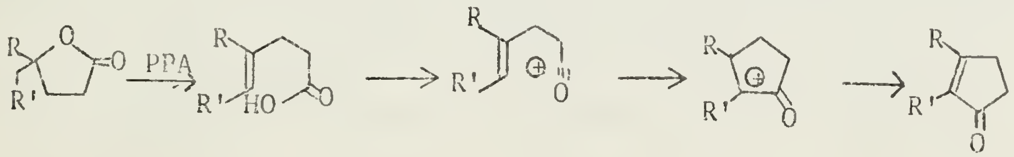
Table IV.[13] Preparation of Cyclobutanones and γ-Lactones

Carbonyl	Cyclobutanone	% Overall Yield	γ-Lactone	% Overall Yield
		97		87
		92		92
		90		85
		95		95
		87		82

γ-Lactones formed from oxaspiropentane intermediates are generally obtained in higher yield and with fewer steps than in other methods of preparation.[13,28] Eschenmoser and co-workers[29] synthesized 36 (Table IV) in three steps from methylenecyclohexane with an overall yield of less than 20%. Trost, using an oxaspiropentane intermediate, made 36 from more readily available cyclohexanone in two steps with 85% yield.

γ-Lactones, when reacted with pyrophosphoric acid, give cyclopentenones.[30] This reaction generally occurs in yields of greater than 90% from the lactone. The mechanism is given in Scheme IX.

Scheme IX



SUMMATION

It can be seen from the reactions given in this review that oxaspiropentanes act as useful intermediates in the transformation of carbonyl compounds into several annulated and acyclic systems. However, in order to demonstrate the overall utility of the method, more work needs to be done, particularly with hindered compounds since prior work has been limited to model systems. Even so, oxaspiropentanes can be considered as offering a new synthetic approach to cyclobutanones, γ-lactones, cyclopentanones, and cyclopentenones.

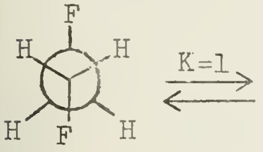
BIBLIOGRAPHY

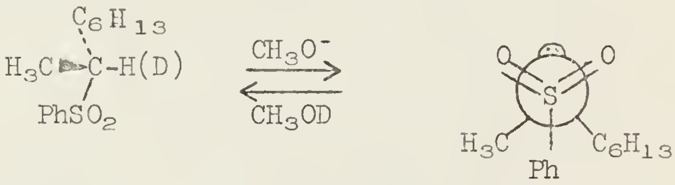
1. J. K. Crandall and D. R. Paulson, J. Org. Chem., 33, 991 (1968).
2. J. R. Salaün and J. M. Conia, Chem. Comm., 1570 (1971).
3. J. R. Wiseman and H. F. Chan, J. Amer. Chem. Soc., 92, 4749 (1970).
4. C. R. Johnson, G. F. Katekar, R. F. Huxoland, and E. R. Janize, J. Amer. Chem. Soc., 93, 3771 (1971).
5. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5311 (1973).
6. M. Korach, D. Nielson, and W. Rideout, J. Amer. Chem. Soc., 82, 4328 (1960); G. B. Payne, Tetrahedron Lett., 763 (1962).
7. C. Rai and S. Dev, J. Indian Chem. Soc., 34, 178 (1957); E. F. Ullman and J. W. Farnshawe, J. Amer. Chem. Soc., 83, 2379 (1971); J. T. Graegson, K. W. Greenlee, J. M. Derfer, and C. E. Boord, ibid., 75, 3344 (1953); H. D. Hartzler, ibid., 81, 2024 (1959); B. C. Anderson, J. Org. Chem., 27, 2720 (1962); R. Köster, S. Arora, and P. Binger, Angew. Chemie, Inter. Ed., Eng., 8, 205 (1969).
8. R. Köster, S. Arora, and P. Binger, Synthesis, 6, 322 (1971).
9. E. E. Schweizer, C. J. Berninger, and J. G. Thompson, J. Org. Chem., 33, 336 (1968).
10. E. J. Corey and M. Chavkovsky, J. Amer. Chem. Soc., 87, 1345 (1965).
11. B. M. Trost and M. J. Bogdanowicz, ibid., 95, 5298 (1973).
12. M. J. Bogdanowicz and B. M. Trost, Tetrahedron Lett., 887 (1972).
13. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5321 (1973).
14. E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 87, 1353 (1965).
15. W. Luttke and K. Wilhelm, Angew. Chemie, Int. Ed., Eng., 4, 875 (1965); D. B. Boyd and R. Hoffmann, J. Amer. Chem. Soc., 93, 1064 (1971).
16. J. M. Townsend and K. B. Sharpless, Tetrahedron Lett., 3313 (1972); A. W. Johnson, "Ylide Chemistry," New York: Academic Press (1966).
17. B. M. Trost and M. J. Bogdanowicz, J. Amer. Chem. Soc., 95, 5307 (1973).
18. C. F. Tang and H. Rapoport, J. Org. Chem., 38, 2806 (1973).
19. J. D. Cox, Tetrahedron, 19, 1175 (1963).
20. (fod) is 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato: R. E. Rondeau and R. E. Sievers, J. Amer. Chem. Soc., 93, 1522 (1971).
21. R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Weinheim, W. Germany: Verlag Chemie, GmbH (1970).
22. M. Hanack and H. J. Schneider, Fortschr. Chem. Forsch., 8, 554 (1967).
23. R. P. Thummel and B. Rickborn, J. Org. Chem., 37, 4250 (1972) and references therein.
24. R. P. Thummel and B. Rickborn, J. Amer. Chem. Soc., 92, 2064 (1970).
25. H. H. Wasserman, H. W. Adickes, and O. Espejo de Ochoa, ibid., 91, 5586 (1971).
26. R. A. Clark, Tetrahedron Lett., 2279 (1971).
27. C. H. Hassal, Org. React., 9, 73 (1957); H. O. House, "Modern Synthetic Reactions," Menlo Park, California: W. A. Benjamin, Inc. (1972).
28. P. L. Creger, J. Org. Chem., 37, 1907 (1972).
29. T. D. K. Gupta, D. Felix, U. M. Kempe, and A. Eschenmoser, Helv. Chim. Acta, 55, 2198 (1972).
30. P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, J. Org. Chem., 37, 1947 (1972).

RATIONALE FOR THE GAUCHE EFFECT

Report by Tyler Thompson November 1, 1973

The "gauche effect", coined by Wolfe[1] but recognized in various forms since the mid-1950's, is a tendency of molecules to adopt that conformation which has the maximum number of gauche interactions between the adjacent electron pairs and/or polar bonds. Thus the gauche form of 1,2-difluoroethane is surprisingly stable. The far-reaching effect of this principle is now seen as being responsible for the highly sterospecific generation and quenching of α-sulfonyl carbanions,[2] and for the stereoselective synthesis of olefins by the Ramberg-Baecklund reaction.[3]



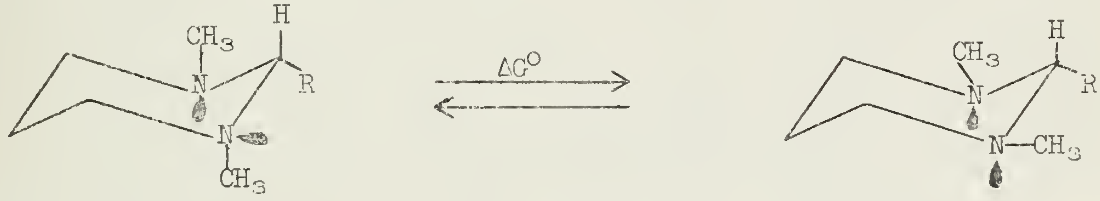


Reliable ab initio calculations on model systems provide the foundation for the gauche effect,[4,5] and reveal important characteristics of lone-pair (lp) and polar-bond (pb) interactions. The relative importance of gauche interactions is pb/pb > pb/lp > lp/lp.[6] Lone electron pairs are more diffuse than bonding electron pairs, and are not properly described as pseudo ligands.[7] The intuitive feeling that lone pairs should exhibit steric repulsion with bonding pairs is not always justified. The two lone pairs on oxygen are better described as a hemispherical electron cloud than as two directed lone pairs.[5] More extensive but less elaborate calculations by Pople[8] generally tend to reinforce Wolfe's results.

While non-empirical calculations demonstrate the gauche effect, they are less helpful in giving the organic chemist an easily grasped rationale for the effect. The best that can be done is to analyze the total energy E of the molecule in terms of the kinetic energy (T), the nuclear and electron repulsions (Vnn and Vee), and the nuclear-electron attraction (Vne):[9]
$E = T + V_{nn} + V_{ee} + V_{ne}$.

An attempt has been made to rationalize the gauche effect in terms of repulsion between lone pairs (nicknamed the "rabbit ear effect"),[10,11] inspired by the discovery that the prefered conformation of the 1,3-diazane I is A rather than B. However, further work showed that this preference is small, and that B is the more stable form of II,[13] so the importance of the rabbit ear effect is in doubt.

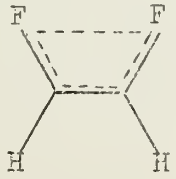
A

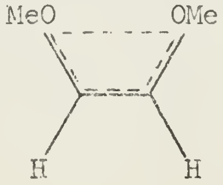


B

I R = CH_3 ΔG^o = +0.13 kcal/mol
II R = H ΔG^o = -0.54 kcal/mol

An elegant explanation for the related stability of cis-1,2-difluoroethylene and cis-1,2-dimethoxyethylene[14] has been proposed by Epiotis,[15] based on the possibility of bonding between the cis-polar substituents. Unfortunately,

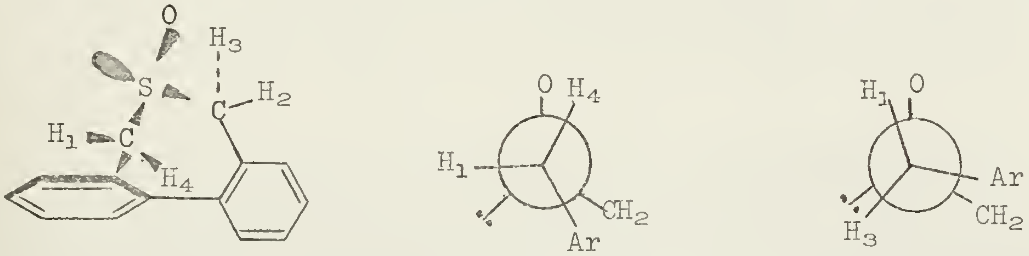




some of the structural predictions of Epiotis's model are at variance with experimentally determined structures.[14,16] Other data support his model.[17] Hoffmann[18,19] has formalized the application of hyperconjugation as a possible stabilizing mechanism.

Finally, it is important to emphasize the limitations of the gauche effect. All of the rationales assume the molecules are in the vapor phase, but it is well known that the conformational equilibria of many polar compounds are highly dependent on solvent. The relative kinetic acidity of the four α-protons in III, for example, completely frustrates the predictions of the gauche effect.[20]

III



REFERENCES

1. S. Wolfe, Accts. Chem. Res., 5, 102 (1972).
2. J. N. Roitman and D. J. Cram, J. Amer. Chem. Soc., 93, 2225, (1973).
3. F. G. Bordwell and B. B. Jarvis, J. Amer. Chem. Soc., 95, 3585 (1973).
4. S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, J. Chem. Soc. B, 136 (1971).
5. S. Wolfe, L. M. Tel, W. J. Haines, M. A. Robb, and I. G. Csizmadia, J. Amer. Chem. Soc., 95, 4863 (1973).
6. S. Wolfe, L. M. Tel, J. H. Liang, and I. G. Csizmadia, J. Amer. Chem. Soc., 94, 1361 (1972).
7. M. A. Robb, W. J. Haines, and I. G. Csizmadia, J. Amer. Chem. Soc., 95, 42 (1973).
8. J. A. Pople, et al., J. Amer. Chem. Soc., 94, 2371 (1972); 95, 693, 699 (1973).
9. L. C. Allen, Chem. Phys. Letters, 2, 597 (1968).
10. E. L. Eliel, Kemisk Tidskrift, 81, no. 6/7, 22 (1969).
11. E. L. Eliel, Angew. Chem. Int. Ed. Engl., 11, 739 (1972).
12. R. O. Hutchins, L. D. Kopp, and E. L. Eliel, J. Amer. Chem. Soc., 90, 7174 (1968).
13. E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Tetrahedron Letters, 3409 (1971).
14. J. T. Waldron and W. H. Snyder, J. Amer. Chem. Soc., 95, 5491 (1973).
15. N. D. Epiotis, J. Amer. Chem. Soc., 95, 3087 (1973).
16. R. P. Blikensderfer, J. H. S. Wang, and W. H. Flygare, J. Chem. Phys., 51, 3196 (1969).
17. E. Saegebarth and E. B. Wilson, J. Chem. Phys., 46, 3083 (1967).
18. R. Hoffmann, L. Radom, J. A. Pople, P. v. R. Schleyer, W. J. Hehre, and L. Salem, J. Amer. Chem. Soc., 94, 6221 (1972).
19. S. David, Odile Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, J. Amer. Chem. Soc., 95, 3806 (1973).
20. R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, J. Amer. Chem. Soc., 94, 8795 (1972).

TETRACYANOQUINODIMETHANE (TCNQ) AND ITS MOLECULAR COMPLEXES

Reported by Gautam Desiraju November 5, 1973

SUMMARY

Tetracyanoquinodimethan(e), (III; TCNQ; 2,5-cyclohexadiene - $\Delta^{1,a,4,a'}$ dimalononitrile) has been known for about ten years.[1] It forms molecular complexes with metallic, organometallic and organic "onium" cations. These complexes have been noted for their unusual electrical and magnetic properties.[2,3] In particular, it has been reported that the 1:1 complex between TCNQ and tetrathiofulvalene (TTF) has a resistivity of 6.8×10^{-5} ohm-cm at 66°K.[4] This seminar will review the chemistry of TCNQ and the chemical and electrical properties of the different types of molecular complexes that it forms.

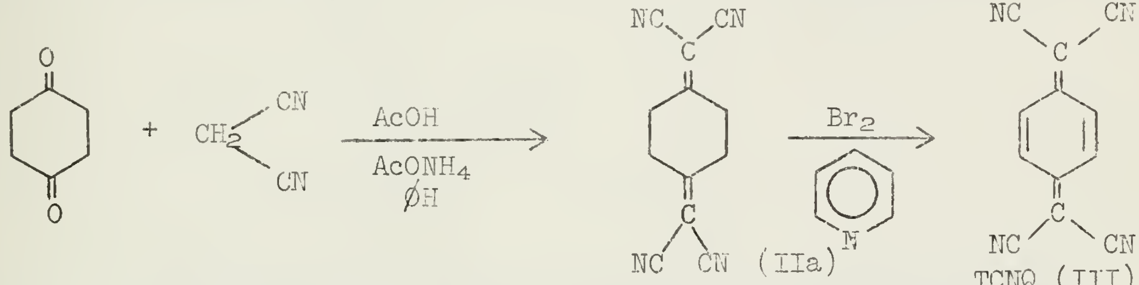
INTRODUCTION

The systematic study of cyanocarbons began essentially in 1958, with the discovery of the first percyanoölefin tetracyanoethylene (TCNE).[5] A cyanocarbon is defined as an organic compound containing only cyano groups attached to the carbon atoms. The earliest known cyanocarbons were dicyanoacetylene and 1,4-dicyanobuta-1,3-diyne.[6,7,8]

On account of the electron withdrawing cyano groups, TCNQ is a strong Lewis acid with an electron deficient π-system. It reacts readily therefore, with electron rich systems (donor systems) to yield adducts and complexes. Although the chemistry of TCNE has been reviewed,[33] we shall briefly be concerned with it here inasmuch as it is a useful comparison to TCNQ. TCNQ is not formally a cyanocarbon since it contains the quinonoid hydrogens; yet its chemical behavior is sufficiently similar to TCNE, to consider both of them together.

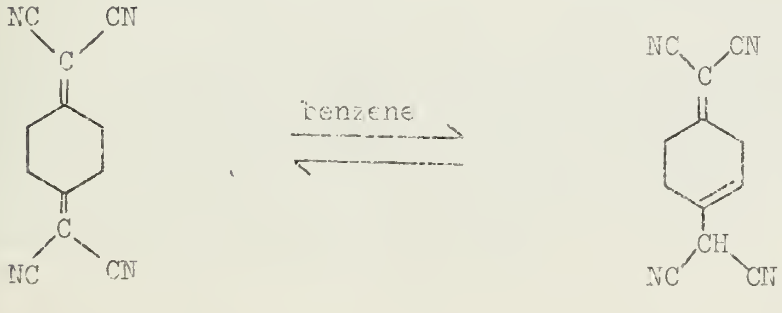
PREPARATION

TCNQ (III) was first synthesised by Acker et al. in 1960.[1] The synthesis involves a condensation between malononitrile and 1,4-cyclohexanedione (I) and dehydrogenation of the product (II a) to give (III). Essentially the same method has been used since.



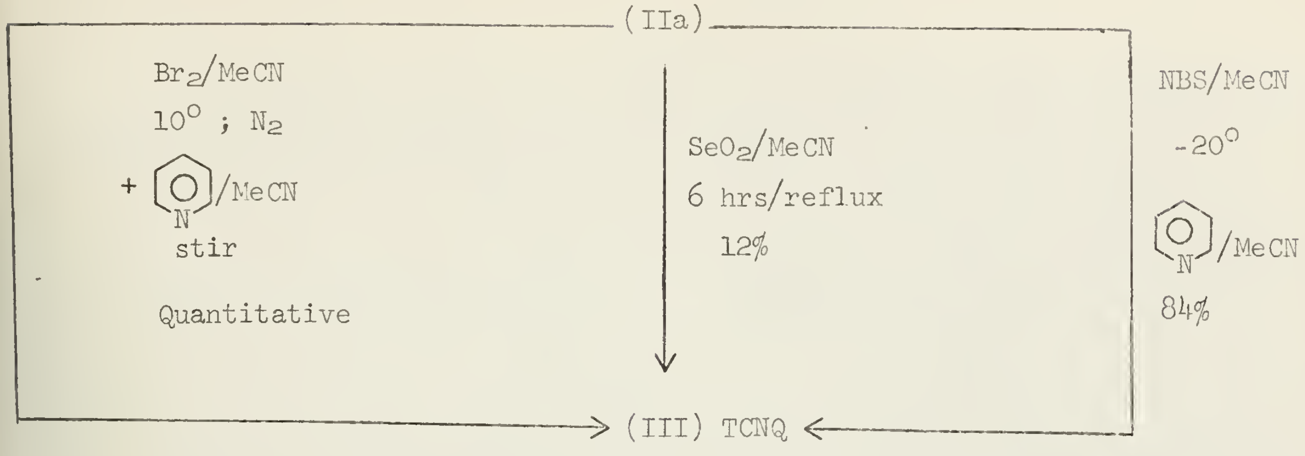
(I) Malononitrile (IIa) TCNQ (III)

1,4-Bis-(dicyanomethylene)-cyclohexane



(II a) (II b)

Later[9] it was found that several dehydrogenating agents could be used.



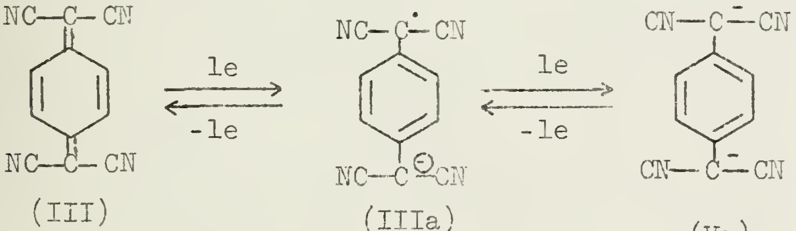
It was originally reported[9] that TCNQ was a rust coloured solid melting at 293-296° and giving yellow to yellow-green solutions in acetonitrile. Later when the preparation was carried out using thoroughly degassed and purified materials, it was found that TCNQ forms brilliant yellow orange crystals which give yellow-orange solutions in acetonitrile.[10]

Most of the important properties of TCNQ and its molecular complexes have been described in a series of papers from DuPont.[9,11,12]

REACTIONS OF TCNQ

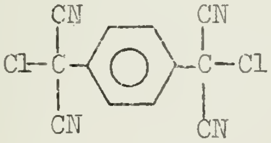
The reactions of TCNQ can be rationalized on the basis of the electron deficiency of its π-system:

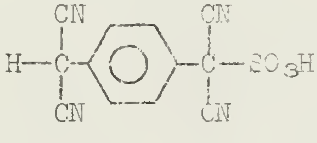
1) It can be reduced to "dihydro-TCNQ" (H_2TCNQ; p-phenylenedimalononitrile, V) with thiophenol, mercaptoacetic acid or hydriodic acid. (V) can be oxidized to TCNQ with N-chlorosuccinimide. The equilibrium TCNQ $\rightleftarrows$ H_2TCNQ has been studied polarographically. These studies show that in an acetonitrile solution containing $LiClO_4$ (0.1M), TCNQ gives two reduction waves with halfwave potentials of +0·127V and -0·291V respectively. These are attributed to the stepwise reduction to semiquinodimethane (IIIa; TCNQ anion radical) and to (Va) respectively.



(III) (IIIa) (Va)

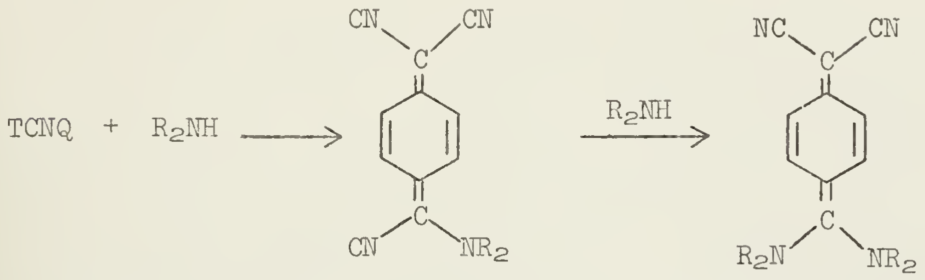
2) It can undergo 1,4 additions with chlorine or sulphur dioxide ($H-SO_3H$) to yield the corresponding 1,4 adducts.





3) TCNQ does not give characterizable Diels-Alder adducts with dienes in contrast to TCNE which does so smoothly. Thus anthracene, cyclopentadiene, or 2,3-dimethylbutadiene react with TCNE to give Diels-Alder adducts while TCNQ gives polymers under the same conditions. However, TCNQ reacts with anthracene to give a π-complex (Type I complex) when hot solutions of the two compounds are mixed and cooled under nitrogen.

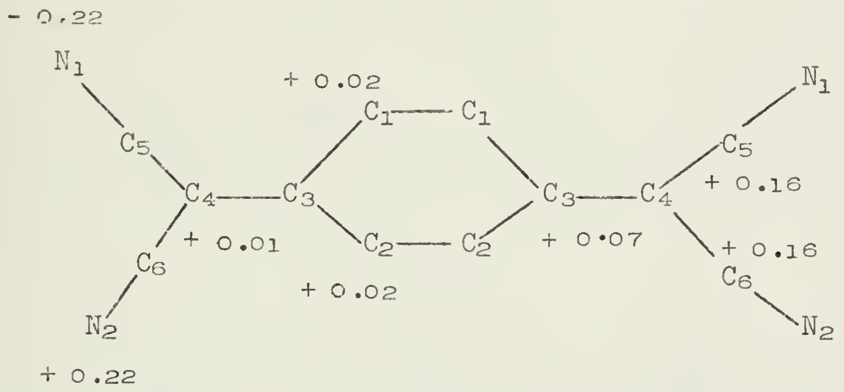
4) TCNQ reacts readily with primary and secondary amines,[12] one or two cyano groups being replaced through nucleophilic substitution:



5) TCNQ reacts with malononitrile in the presence of base to give a deeply coloured anion.[35]

MOLECULAR COMPLEXES OF TCNQ

TCNQ forms a large number and variety of molecular complexes with several types of donors.[11] The TCNQ molecule is especially well adapted to the formation of crystalline complexes since the molecule is planar and can pack easily into the crystal lattice of the complex. The four electron withdrawing cyano groups attached to the delocalized system of π-orbitals lead to an electron deficient π system. Results of an MO calculation on TCNQ give the effective charge on each of the atoms.[13]



Molecular complexes of TCNQ are included in the broad group of charge transfer complexes. Complexes of this type are very well known[14,15] and there are many detailed accounts and reviews of their properties.[16,17] The formation of these complexes involves a transfer of electron density from one of the species (donor) to the other (acceptor). Charge transfer complexes involving two conjugated π systems are very common. In the now classical paper, Mulliken[17] has given the first MO description of charge transfer complexes. According to him, the formation of a charge transfer complex involves a shift of an electron from the highest occupied molecular orbital (HOMO) of the donor to the lowest unoccupied molecular orbital (LUMO) of the acceptor. For maximum charge transfer interactions, the relative orientations of the molecules should give maximum overlap of the filled orbitals (donor) with the vacant orbitals (acceptor). Several other parameters have been used to compare the electron affinity of TCNQ with respect to other acceptors.[18]

It should, however, be noted that the fact that a charge transfer complex is formed, does not necessarily imply that the complex will be paramagnetic. The shift of electron density from donor to acceptor may or may not involve an unpairing of spins. Thus, correlations between paramagnetic susceptibilities and electrical conductivity are difficult to make.

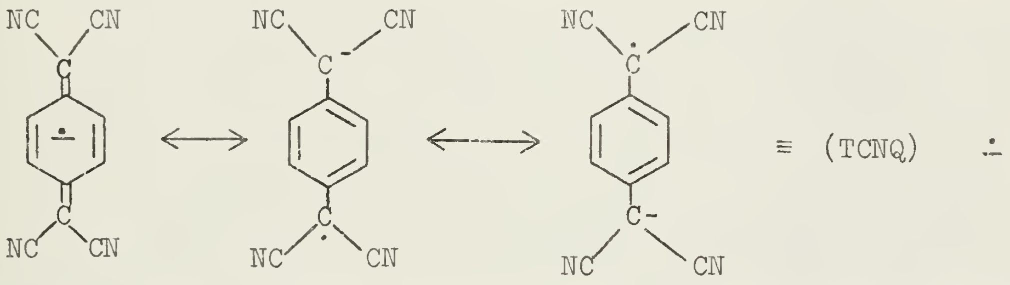
TCNQ forms three basic types of molecular complexes:

"Type I" complexes or π-complexes are formed with aromatic hydrocarbons, aromatic amines and polyhydric phenols. The complexes are of the form (donor):(TCNQ) generally in a 1:1 ratio. Complexes of this type are also formed with donor species by other electron deficient molecules such as chloranil and TCNE.

These complexes are readily isolated because of their low solubilities. They can be readily prepared by mixing hot solutions of the donor and TCNQ. The solvents generally used are chloroform, methylene chloride or dioxane. If the starting materials are analytically pure, the complex is also pure. The complexes dissociate and/or decompose on heating. Recrystallization of the complex often results in its dissociation.

Typical examples of π-complexes prepared include (TCNQ) (anthracene), (TCNQ) (p-phenylene diamine) and (TCNQ) (N,N'-tetramethyl-p-phenylene diamine).

"Type II" complexes. In these complexes, the TCNQ moiety carries a formal negative change. Visible and UV absorption spectroscopy seems to indicate that the species in solution is the TCNQ radical anion. This anion is quite stable (resonance stabilized).



The cations in these complexes are usually metals and the complexes are of the general form $M^{+n}(TCNQ^{\cdot -})_n$. Occasionally, an organic "onium" ion forms Type II complexes.

The complexes are usually red or purple crystalline solids when the cation itself is not chromophoric. They are conveniently prepared by treatment of a solution of TCNQ with a solution of the metal iodide, MI.

$$TCNQ + I^- \longrightarrow TCNQ^{\cdot -} + \tfrac{1}{2} I_2$$

$$TCNQ^{\cdot -} + M^+ \longrightarrow M^+(TCNQ)^{\cdot -}$$

$$I_2 + I^- \longrightarrow I_3^-$$

Caesium iodide is exceptional in that it gives the complex $Cs_2^{2+}(TCNQ^{\cdot -})_2(TCNQ)$ rather than the Type II complex $Cs^+(TCNQ^{\cdot -})$. These complexes are characterized by their very low solubilities. The only important Type II complex having an appreciable (1%!) solubility in acetonitrile is the lithium complex $Li^+(TCNQ)^{\cdot -}$ (VI). Thus, this is a very convenient precursor in the preparation of various metal-ion-$TCNQ^{\cdot -}$ complexes.

$$\begin{tikzcd}
Ag^+(TCNQ)^{\cdot -} & \underset{(VI)}{Li^+(TCNQ)^{\cdot -}} \arrow[l, "Ag^+"'] \arrow[r, "Fe^{2+}"] \arrow[d, "Et_3N^{\oplus}"] & Fe^{2+}(TCNQ^{\cdot -})_2 \\
 & Et_3N^+(TCNQ)^{\cdot -} &
\end{tikzcd}$$

The solutions of the soluble complexes in solvents like alcohol or acetonitrile exhibit a change in colour on dilution. Concentrated solutions of (VI) are blue, but on dilution, turn green. This has been ascribed to the presence of two species in solution : the dimer $(TCNQ^{\cdot -})_2$ at higher

concentrations and the monomer $(TCNQ)^{\dot{-}}$ at lower concentrations.[19] Mineral acids decompose the Type II complexes into neutral TCNQ and H_2TCNQ.

$$M^{+}(TCNQ)^{\dot{-}} + H^{\oplus} \longrightarrow (HTCNQ)^{\bullet} \xrightarrow[\text{oxidation}]{\text{auto}} \tfrac{1}{2}\,TCNQ + \tfrac{1}{2}\,H_2TCNQ$$

The infrared spectra of these complexes show very strong absorptions in the 1 to 1.5 μ region ascribed to electronic rather than vibrational absorptions. Polarographic studies on the $TCNQ^{\dot{-}}$ radical anion have been carried out on Type II complexes in solution as described previously for TCNQ itself.

ESR studies on the solutions of these complexes indicated that the green solutions (mainly monomer) of the complexes show a stronger ESR signal than the blue solutions (mainly dimer). The paramagnetism of the species in the blue solutions increases on heating, indicating that the diamagnetic dimer is converted into the paramagnetic monomer.

"Type III" complexes. In these complexes there is, associated with each charge transfer pair of donor and acceptor, a formally neutral molecule of TCNQ. They can be thus represented as $M^{+}(TCNQ)^{\dot{-}}(TCNQ)$ where M^{+} is typically some organic cation. A few complexes of the type $M_2^{+}(TCNQ^{\dot{-}})_2(TCNQ)$ have also been reported.[11]

UV and visible spectra indicate that both (TCNQ) and $(TCNQ)^{\dot{-}}$ exist in solution. But the high conductivity of the solid complexes would seem to indicate that there is extensive delocalization of the negative charge over the TCNQ molecules. This might also be inferred on the basis of the crystal structures of these complexes,[20,21] since, bond lengths in the TCNQ units were intermediate between those found for $TCNQ^{\dot{-}}$ and TCNQ.

Type III complexes of TCNQ have been prepared for a large variety of cations : methyl and aryl substituted ammonium, phosphonium, arsonium, stibonium, sulphonium and oxonium ions.[9] Four major routes have been used to prepare these complexes:

a) Treatment of the simple salt (Type II complex) with excess TCNQ

$$(Et_3NH)^{+}(TCNQ)^{\dot{-}} + TCNQ \xrightarrow[50\%]{MeCN} (Et_3NH)^{+}(TCNQ)_2^{\dot{-}} \quad \text{VII}$$

The method is obviously applicable only when the corresponding Type II complex is available. The method is irreversible and free TCNQ connot be recovered from the complex by solution, sublimation etc.

b) Reduction by iodide ion

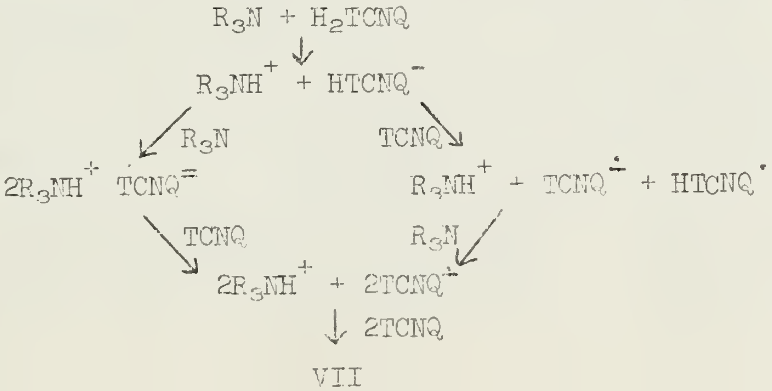
$$3Et_3\overset{+}{N}H\,\overset{-}{I} + 2TCNQ \xrightarrow[50\%]{MeCN} \text{VII}$$

The stoichiometry of the reactants is such that all the iodine formed is scavenged as I_3^-. This method is generally applicable for all "onium" iodides (except morpholinium iodide which forms a Type II complex).

c) Use of H_2TCNQ as a proton and electron donor.

$$2Et_3N + H_2TCNQ + 3TCNQ \xrightarrow[90\%]{MeCN} \text{VII}$$

Two alternative routes exist for the formation of VII; (R = Et).



d)

$$Et_3N + 2TCNQ \xrightarrow[77\%]{MeCN} VII$$

Two routes again are possible for the formation of VII

$$Et_3N + TCNQ \longrightarrow CH_3CH = \overset{+}{N}Et_2 + HTCNQ^- \xrightarrow{TCNQ, 2Et_3N} CH_2 = CH\text{-}NEt_2 + 2[Et_3NH^+ \; TCNQ^{\dot{-}}]$$

$$CH_2 = CH\text{-}NEt_2 + 2[Et_3NH^+ \; TCNQ^{\dot{-}}] \xrightarrow{2TCNQ} VII$$

$$Et_3N + TCNQ \longrightarrow Et_3\dot{N}^+ + TCNQ^{\dot{-}} \xrightarrow{Et_3N} Et_3NH^+ TCNQ^{\dot{-}} + CH_3\dot{C}H\text{-}NEt_2$$

$$\xrightarrow{Et_3\dot{N}^+ \; TCNQ^{\dot{-}}} 2[Et_3NH^+ \; TCNQ^{\dot{-}}] + CH_2 = CHNEt_2 \xrightarrow{2TCNQ} VII$$

Both routes are presumed to involve the intermediate formation of a vinylamine, but these have not been detected so far.

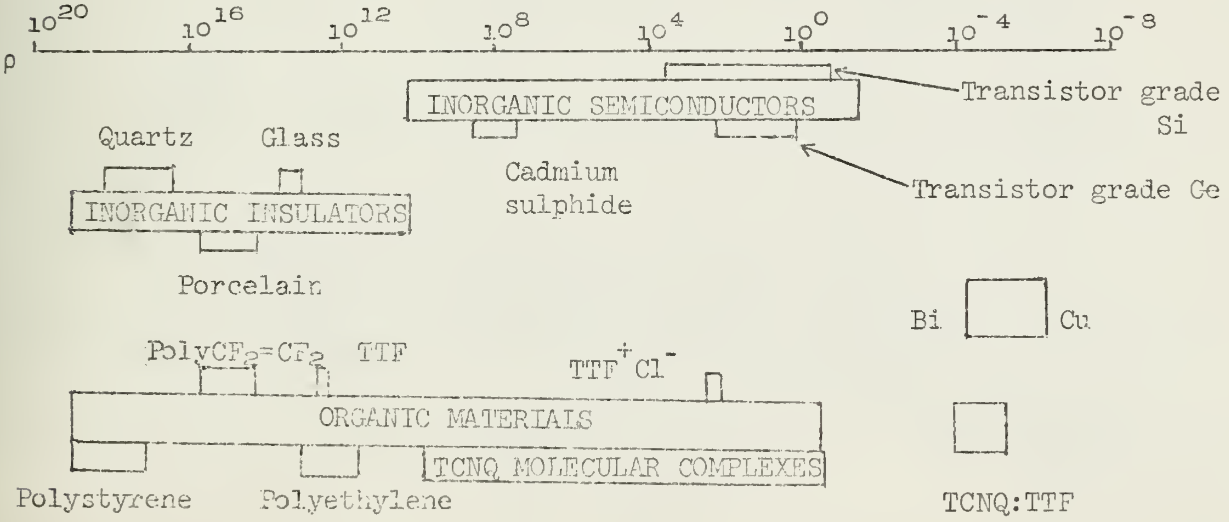
Type III complexes are very stable. They can be recrystallised from acetonitrile without change in form. Mineral acids, however, will decompose them to free TCNQ and H_2TCNQ. Polarographic studies on solutions of these salts give similar results to those already described.

ELECTRICAL AND MAGNETIC PROPERTIES OF TCNQ COMPLEXES

Many TCNQ complexes, of all three types, show interesting electrical and magnetic phenomena. Many of these complexes are good conductors as compared to typical organic materials and may be loosely classified as compounds of intermediate conductivity. The conductivity or rather its reciprocal, the resistivity is generally used to measure the ease of conduction.

$$\text{Resistivity} = \rho = \frac{RA}{l} \text{ ohm-cm} \quad R \text{ in ohm} \quad l \text{ in cm} \quad A \text{ in cm}^2$$

Most of these complexes behave as semiconductors. A semiconductor is defined as a compound which exhibits an exponential variation of its resistivity with temperature. Silicon, a typical inorganic semiconductor has a resistivity of 10^3 ohm-cm at room temperature. Almost all organic substances are insulators ($\rho = 10^{10}$ to 10^{14} ohm-cm). Metals, which are the best conductors, have a resistivity of approximately 10^{-6} ohm-cm. The following table[22] should give some indication of the relative conductivities of various organic and inorganic materials.

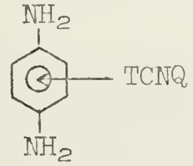


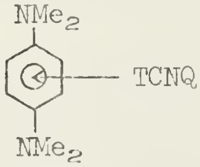
It is difficult to correlate results of ESR experiments with the conductivities of TCNQ complexes. Generally it is found that the high conductivity complexes show a temperature independant paramagnetism.[2] The formation of the charge transfer complex could lead to either a diamagnetic singlet state or a paramagnetic triplet state. Since the complex does not necessarily have to be paramagnetic to show a high conductivity, correlations of electrical and magnetic properties remain at best, confusing.[3]

Type I Complexes are characterized by intermediate to high resistivities (ρ = 10^4 to 10^{12} ohm-cm). These complexes show very weak EPR signals. It is found that the complexes of TCNQ with aromatic amines are the most highly conducting among the Type I complexes. However, there is no general correlation between the basicity of the donor and the resistivity of the complex.

Impurity and steric effects often play very important roles in the conducting process. Since these effects are not crucial for the formation of a paramagnetic species, correlation between ESR[23] and conductivity measurements becomes even less pronounced.

eg.,





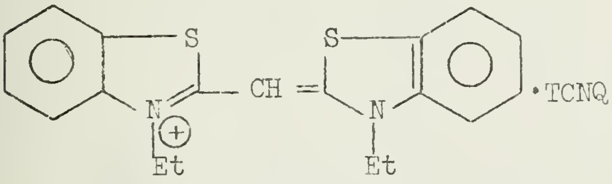
ρ	10^3 ohm cm	10^9 ohm cm
EPR	4×10^{20}	4×10^{21} (unpaired electrons per mole of acceptor-donor pairs)

Structure determination[24] of the Type I complexes show that, in the solid, there are alternating stacks of TCNQ and donor molecules.[25]

Type II Complexes These compounds are characterized by intermediate to high resistivities (ρ = 10^2 to 10^5 ohm-cm for metal-TCNQ complexes: ρ = 10^2 to 10^7 ohm-cm of organic cation-TCNQ complexes). These complexes also show weak EPR absorption in the solid. The conductivities are isotropic (identical along the three crystallographic axes).

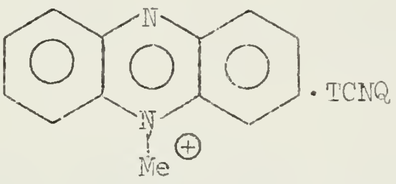
A few Type II complexes of TCNQ, with organic "onium" ions, however, show high conductivities. The 1:1 complex (TCNQ) (5,8-dihydroxyquinoline) has a resistivity of 15 ohm-cm at room temperature.[11] This is a value rather similar to that for the conducting Type III complexes. Other compounds of this type include, (dibenzenechromium):(TCNQ), (3,3 diethylthiacyanine):(TCNQ), VIII; (N-methylphenazine) (TCNQ) IX; (tetrathiofulvalene) (TCNQ) X.

VIII

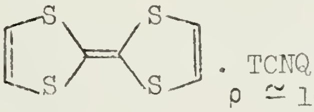


ρ = 7×10^{-3} ohm-cm

IX



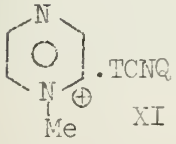
ρ = 7×10^{-3} ohm-cm



X

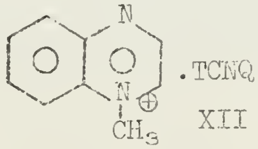
$\rho \simeq 10^{-5}$ (at 60K)

But apparently similar Type II complexes have much lower conductivities



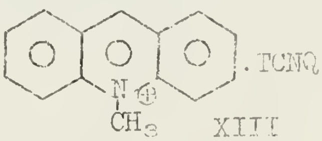
XI

ρ = 3.4×10^7 ohm-cm



XII

ρ = 126 (?)



XIII

ρ = 10^9 ohm-cm

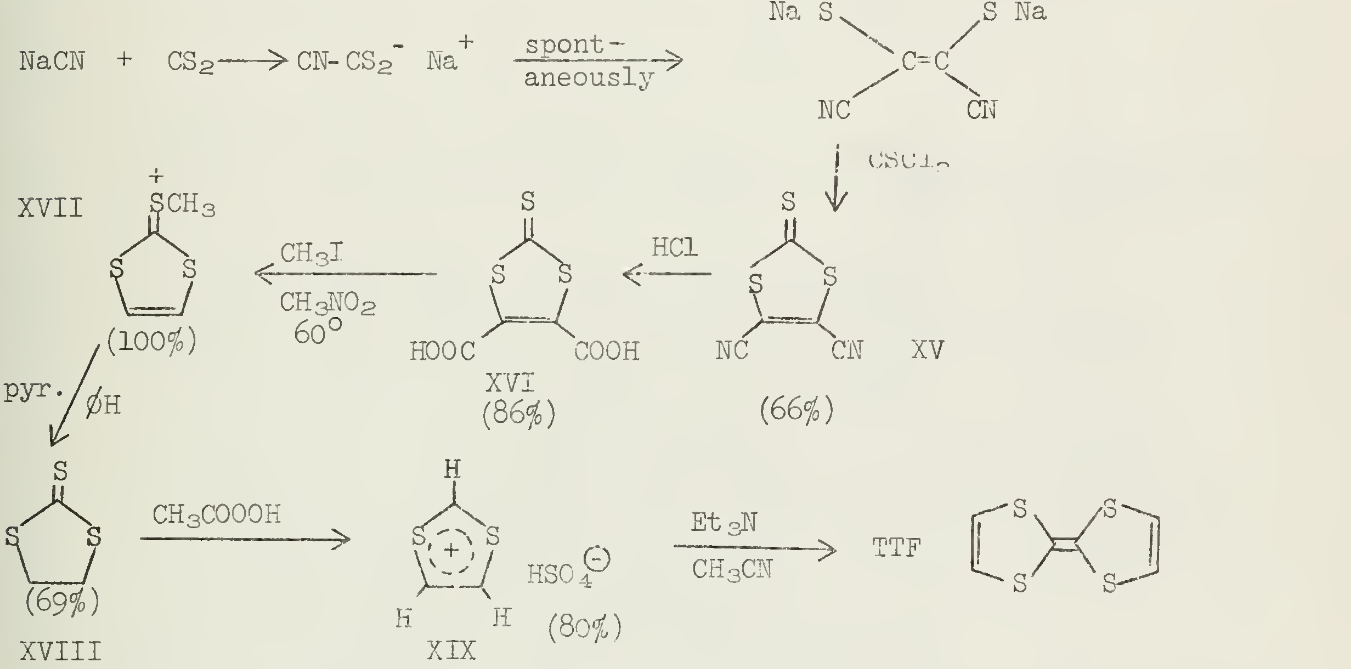
Structure determination of these complexes indicate that there are two types of possible arrangements: The TCNQ$^{\cdot}$ molecules can be arranged in stacks parallel to one of the crystal[26] axes or they can be localized in smaller stacks so that there are no distinct anion planes.[27] The former variety is characterized by moderate to high conductivities and the latter by lower conductivitie

Type III complexes. The delocalization of the radical character over two molecules of TCNQ per each charge transfer set is believed to cause the generally increased conductivities of Type III complexes as compared to Type I and Type II complexes. The resistivities for many of these compounds is in the 10^{-2} to 10^{2} ohm-cm range. These also show the exponential temperature dependence of resistivity, characteristic of semiconductors. The electrical conductivities are anisotropic and differ by several orders of magnitude along the three major crystallographic axces.[11] ESR studies on a series of Type III complexes,[2] do not indicate any clear correlation between paramagnetic susceptibility and electrical conductivity.

Structure determination of the more highly conducting complexes show the presence of infinite stacks of TCNQ molecules[21] (radical ions and neutral species). Where the stacks are not formed (or are localized) the conductivity is lower.[20]

The TCNQ-TTF complex. This 1:1 molecular complex between TCNQ and TTF (tetrathiofulvalene), X, has recently attracted wide attention when certain superconducting possibilities were ascribed to it by Heeger et al.[34]

The TTF and TTF cation systems have been known to be good conductors.[28] The synthesis of TTF from NaCN and CS_2 via 1,3 dithiolium hydrogen sulphate, XIX, has been described.[29, 30, 31, 32]



Prior to this, the highest conductivity reported for an organic compound was for the N-methylphenazium (NMP) - TCNQ complex, IX.[10] It was reported by Ferraris et al. that X had a conductivity of 1.47×10^{4},[4] $(\text{ohm-cm})^{-1}$ at 66°K. These workers suggested that X behaved like a metal over large temperature ranges. Heeger et al.[34] reported that the conductivity at 66°K was much higher than this value, being almost 500 times the value at room temperature. Their reported conductivity at 58°K was $10^{6} (\text{ohm-cm})^{-1}$ (i.e., $\rho = 10^{-6}$ ohm-cm). For comparison, the room temperature conductivity of copper is 6×10^{5} $(\text{ohm-cm})^{-1}$ [$\rho = 1.7 \times 10^{-6}$ ohm-cm]. They accounted for this extraordinary value, partly on the basis of the small size and large polarizability of the cation, the latter being presumably due to the sulphur heteroatoms.

Yet, Bloch et al. reported that there is no evidence for these high temperature superconducting fluctuations. They also pointed out that the earlier results represented measurements on only three crystals out of the seventy originally tried.

The field of organic superconductors at high temperatures is obviously of some importance. Even if the results reported above are still inconclusive, TCNQ complexes are likely to be more and more important as semiconductors. The unique properties of TCNQ have already opened up this new and exciting field.

BIBLIOGRAPHY

1. D. S. Acker, R. J. Harder, W. R. Hertler, W. Mahler, L. R. Melby, R. E. Benson and W. E. Mochel, J. Amer. Chem. Soc., 82, 6408 (1960).
2. W. J. Siemons, P. E. Bierstedt and R. G. Kepler, J. Chem. Phys., 39, 3523 (1963).
3. R. G. Kepler, ibid., 39, 3528 (1963).
4. J. Ferraris, D. O. Cowan, V. Walatka and J. H. Perlstein, J. Amer. Chem. Soc., 95, 948 (1973.
5. T. L. Cairns et al., ibid., 80, 2775 (1958).
6. C. Moureu and J. Bongrand, Ann. Chim., 14, 47 (1920).
7. C. Moureu, Compt. rend., 170, 1025 (1928).
8. F. J. Brockman, Can. J. Chem., 33, 507 (1955).
9. D. S. Acker and W. R. Hertler, J. Amer. Chem. Soc., 84, 3370 (1962).
10. L. B. Coleman et al., Phys. Rev. B, 7, 2122 (1973).
11. L. R. Melby et al., J. Amer. Chem. Soc., 84, 3374 (1962).
12. W. R. Hertler et al., ibid., 84, 3387 (1962).
13. H. E. Long et al., Acta Cryst., 18, 932 (1965).
14. H. Schlenk, Ann., 368, 277 (1909).
15. P. Pfeiffer, "Organische Molekulverbindungen", 2nd ed., Stuttgart, (1927).
16. R. Foster, "Organic Charge Transfer Complexes", Academic Press, N. Y. (1969).
17. R. S. Mulliken, J. Amer. Chem. Soc., 74, 811 (1952).
18. S. A. Berger, Spectrochim. Acta, 23, 2213 (1967).
19. L. Michaelis and S. Granick, J. Amer. Chem. Soc., 65, 1747 (1943).
20. P. Goldstein et al., Acta Cryst., 24, 778 (1968).
21. C. J. Fritchie and P. Arthur, ibid., 21, 139 (1966).
22. S. C. Datt, J. K. D. Verma and B. D. Nag, Sci. Cult., 32, 57 (1966).
23. L. R. Melby, Can. J. Chem., 43, 1448 (1965).
24. R. B. Shibaeva and L. O. Atovmyan, Zh. Strukt. Khimii, 13, 546 (1972).
25. R. M. Williams, Acta Cryst., 24, 168 (1968).
26. E. B. Yagubskii et al., Izv. Akad. Nauk SSSR Ser. Khim., 2124 (1968).
27. P. Arthur, Acta Cryst., 17, 1176 (1964).
28. F. Wudl, J. Amer. Chem. Soc., 94, 670 (1972).
29. R. Mayer and B. Gebhardt, Chem. Ber., 97, 1298 (1964).
30. G. Bähr and G. Schlutzer, ibid., 90, 438 (1957).
31. E. Klingsberg, J. Amer. Chem. Soc., 86, 5290 (1964).
32. F. Wudl et al., Chem. Comm., 1453 (1970).
33. D. N. Dhar, Chem. Rev., 67, 611 (1967).
34. L. B. Coleman, M. J. Cohen, D. J. Sandman, F. G. Yamagishi, A. F. Garito and A. J. Heeger, Sol. St. Comm., 12, 1125 (1973).
35. J. K. Williams, J. Amer. Chem. Soc., 84, 3478 (1962).

AFFINITY CHROMATOGRAPHY

Report by Hansen M. Hsiung November 8, 1973

INTRODUCTION

Conventional methods of protein purification utilize fractionation (precipitation by ammonium sulfate) centrifugation, chromatographic methods and electrophoresis. All these methods are general and nonspecific techniques of protein purification, which utilize the subtle differences in physical-chemical properties of various proteins (e.g., solubilities, charge distribution, size and shape etc.). A new technique, "affinity chromatography", exploits the unique biological properties of macromolecules to bind their ligands specifically and reversibly. By this method, the impure protein mixture is passed through a specially prepared column which contains a specific covalently bound "ligand" on an insoluble support. Since the active site of the desired protein will bind with this "ligand" specifically and reversibly, the desired protein is retarded in the column, whereas impurities are washed through the column. The purified protein can be released from the column by changing the pH or ionic strength of eluent or by adding soluble "ligand" to compete with the insoluble "ligand".

This seminar will deal briefly with the basic principle of affinity chromatography, more thoroughly with preparations of the ligand-support complexes and finally will survey the most recent work on the applications of affinity chromatography in solving problems of scientific and practical interest.

SELECTION OF SOLID SUPPORT

Solid support is the skeleton of affinity chromatography. An ideal solid support for affinity chromatography must possess the following properties:[1,2,3,4] a) It must have no interactions with proteins in general to minimize nonspecific adsorption of the proteins, b) it should have a very loose, porous network to allow large macromolecules to pass uniformly through the entire matrix, c) it must possess some functional group that can be modified to allow the covalent attatchment of a variety of ligands, d) it must be chemically and mechanically stable to some relatively drastic conditions of pH, ionic strength, temperature and the presence of denaturants which may be required in elution.

Various organic and inorganic substances have been used as solid supports for affinity chromatography. They include cellulose, polystyrene, polyacrylamide, agarose and porous glass. Hydrophilic cellulose derivatives have been used successfully as solid supports in a few cases,[5] but generally they are not very desirable because their fibrous nonuniform character impedes the proper penetration by large protein molecules. Polystyrene is a highly hydrophobic polymer and displays poor communication between the aqueous and solid phases. Commercially available crossed-linked dextran derivatives such as Sephadex possess many of the previously mentioned desired properties but exhibits a low degree of porosity. Synthetic polyacrylamide gels have many desired features and are available commercially in beaded, spherical forms (Bio-Gel, Bio-Rad Laboratories). The porosity of Bio-Gel is usually lost during the chemical modifications which are required for "ligand" attachment. In the past few years,[1,29] a new beaded porous polysaccharide, agarose, has been widely used as a solid support for affinity chromatography. These beaded agarose derivatives, now commercially available under the trade names Sepharoses, have nearly all the properties desired of a solid support. More recently, Weetall and Hersh[7,8] have found porous glasses suitable for affinity chromatography. They have used porous glass to immobilize "ligands" and "enzymes" and porous glasses seem to have a very promising future.

SELECTION OF THE "LIGAND"

To function, a ligand must be a compound which is tightly and specifically bound to the enzyme (or other macromolecules which is to be purified). Choices of ligands usually fall into the following categories: a) substrates and competitive inhibitors, b) effectors and non-competitive inhibitors, c) coenzymes. Cuatrecasas[2] has shown that successful purification, in particular with low molecular weight competitive inhibitors, depends on the order of magnitude of the inhibition constant (K_i) and above all, on the distance between the inhibitor and solid support polymer matrix. Lowe et al[9] point to the important aspect of maintaining the original conformation of bound molecules. The thermodynamics of binding between "ligand" and "enzyme" can be shown in a simple manner.

$$E + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EL \qquad K_d = \frac{[E]\,[L]}{[EL]} \qquad \Delta G_d = -RT \ln K_d$$

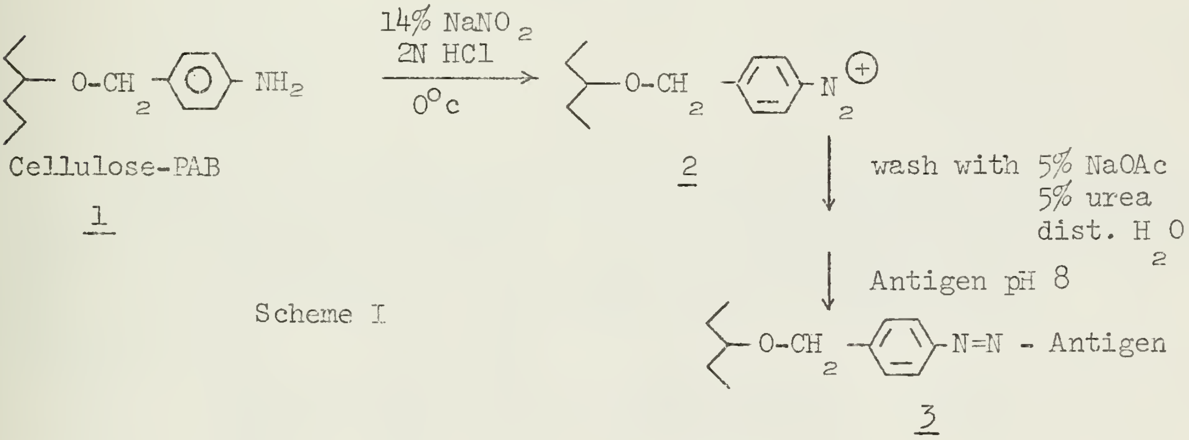
K_d=dissociation constant of ligand from enzyme
ΔG_d=Free energy change of dissociation

Successful affinity chromatography usually requires K_d in an order of 10^{-5} to 10^{-7} M. The important parameter is the effective affinity between the immobilized "ligand" on the surface of the support and free "macromolecules" in solution. To make a "ligand" more accessible to the binding sites of the enzymes, a long "arm" between "ligand" and "solid support" is usually required. This "arm" is usually a hydrocarbon chain. The hydrophobic "arm" may bind non-specifically to the proteins,[10] Although to be successful, affinity chromatography should exclude this non-ideal behavior.

PREPARATIONS OF COVALENT LINKAGE BETWEEN "LIGAND" AND "SUPPORT"

1. Cellulose and polystyrene

Campbell et al.[11] have coupled a soluble protein antigen to an insoluble, modified (p-aminobenzyl) cellulose by means of a diazo bond. This provides an insoluble protein antigen which can specifically combine with its antibody and which will, upon acidification to pH 3.2, release the soluble antibody that can then be separated from insoluble antigen by centrifugation. The yield of antibody recovered is 57% and the purity is more than 90%. (Scheme 1)



Scheme I

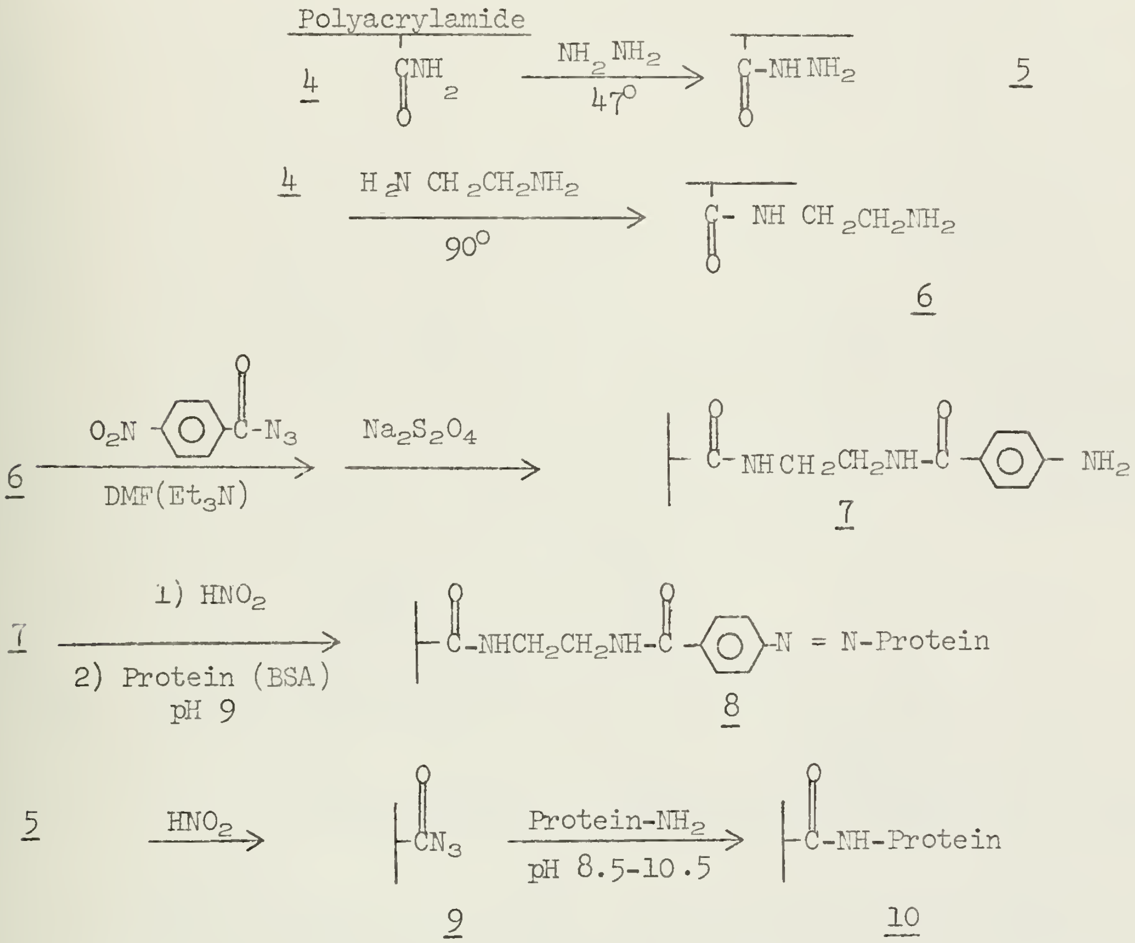
Antigens have been coupled to carboxymethyl cellulose to form carboxamide linkage using dicyclohexylcarbodimide (DCC) in organic solvents.[12] Proteins have been coupled to insoluble polystyrene and cellulose supports

by reactions involving acyl halides, sulfonyl halides, acid anhydrides and acyl azides.[13,14] Nucleotides have been linked by carbodiimide reagents to cellulose through phosphoester bonds in aqueous and organic solvents.[15,16,17]

2. Polyacrylamide

Polyacrylamide beads have been used extensively for gel filtration and solid support in gel electrophoresis. Inman and Dintzis[18] devised several chemical procedures for preparing polyacrylamide-ligand complexes. They coupled bovine serum albumin to polyacrylamide beads (4) and isolated rabbit antibodies to bovine serum albumin by affinity chromatography.

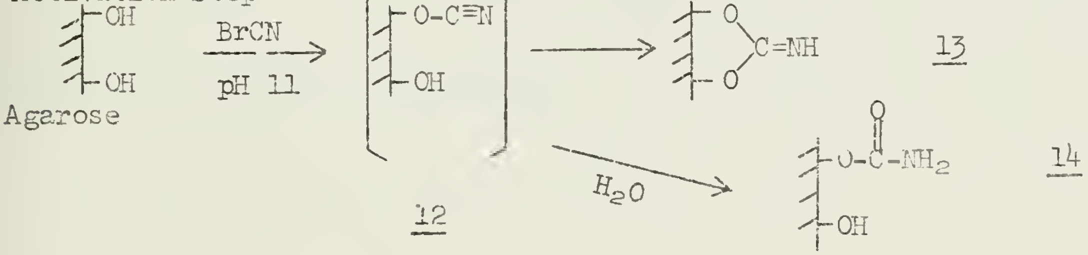
Scheme II



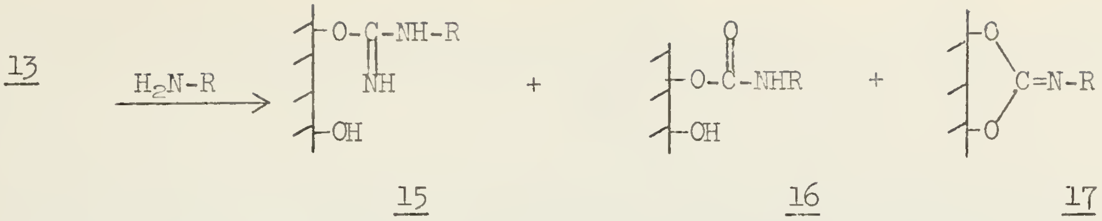
3. Agarose

Agarose with the trade name Sepharose, is a polysaccharide composed of anhydrogalactose and galactose.[19] In order for ligands to be attached, agarose (11) has to be activated. This is accomplished by treatment with cyanogen bromide at high pH (pH 10-11).[20] This activated agarose will react with ligands which contain primary amino groups. (Scheme III)

Scheme III
Activation Step

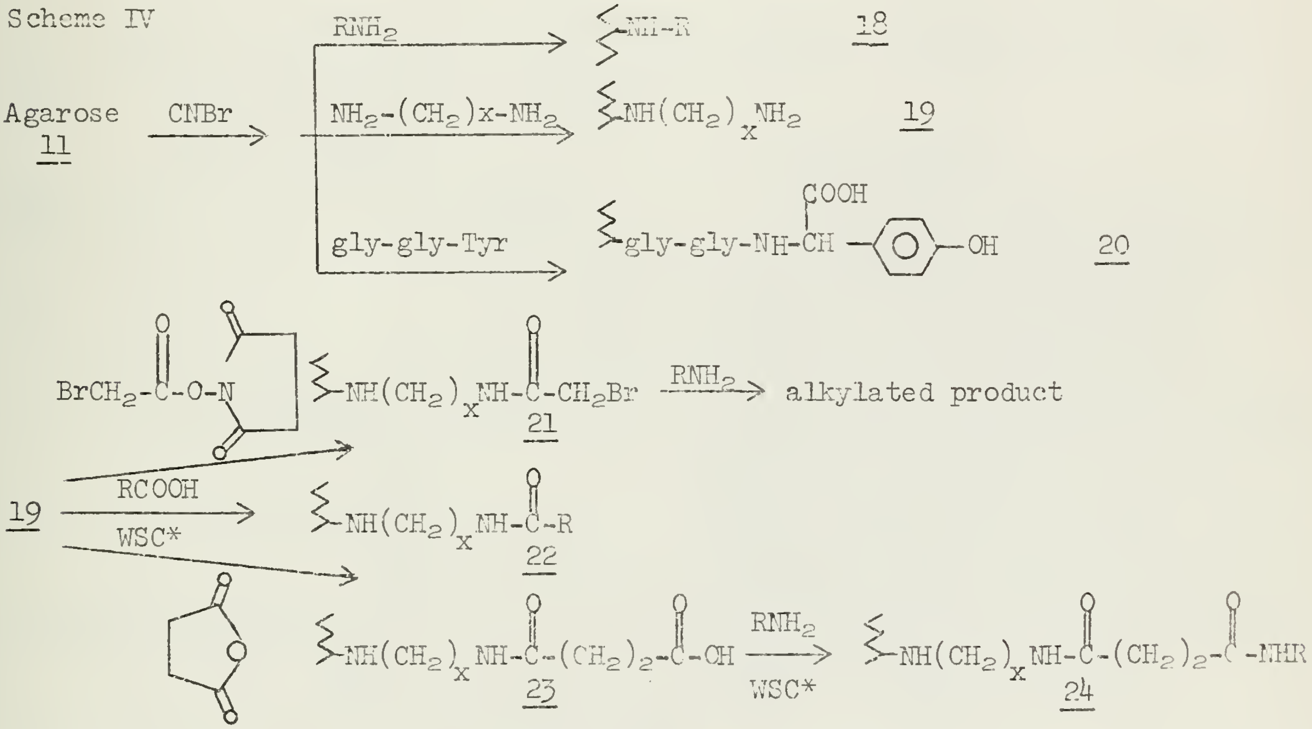


Coupling Step

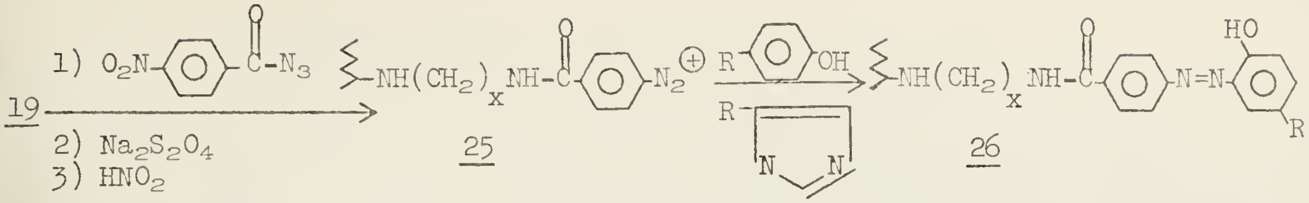


The organic chemical basis of the activation process has been studied[20] mainly in the case of Sephadex, but probably the same reactions are involved for other polysaccharides as well. The treatment of Sephadex or agarose (11) with cyanogen bromide results in the formation of imidocarbonates (13) and carbamic acid esters (14) of polysaccharides. Molecule 14 is stable, inert and neutral and compound 13 is probably responsible for most of the coupling capacity. The organic chemical basis for the coupling reaction has been studied with model compounds. Ethyl imidocarbonate (13) was allowed to react in aqueous solution with amino acids or amino acid derivatives. The main products are N-substituted isoureas (15), N-substituted carbamic acid esters (16) and N-substituted imidocarbonates (17). The reaction of activated agarose with "ligand" or "arm" molecules was accomplished in aqueous soltuion at neutral or slightly basic conditions. Under these conditions, macromolecules can maintain their native conformation unchanged and thus preserve their biological properties intact. Cuatrecasas[1,29] used classical methods of organic chemistry to prepare many derivatives of agarose with different ligands attached to it. He also attached to the activated agarose various compounds that function as an "arm" between ligands and solid supports. These "arm" molecules have functional groups which can be further coupled to "ligands" for affinity chromatography. (Scheme IV)

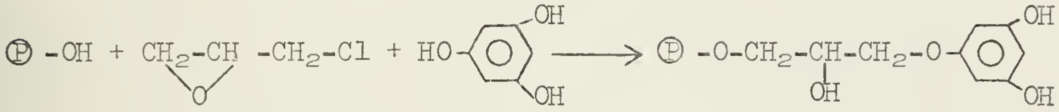
Scheme IV



*WSC - Water soluble carbodiimide

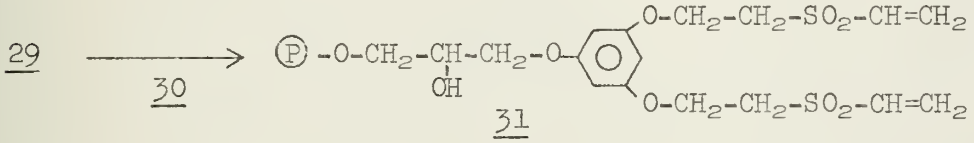


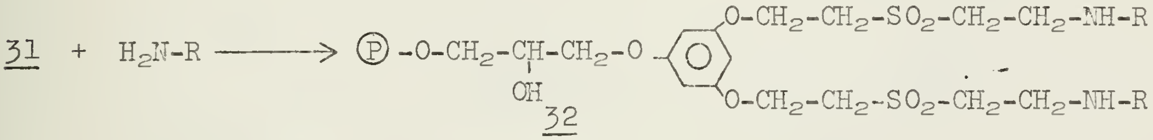
A new coupling reaction has been devised for ligand attachment and enzyme immobilization. Porath et al.,[23] have used epichlorohydrin (27) to link phloroglucinol (28) to the insoluble support, agarose (11).



11 27 28 29

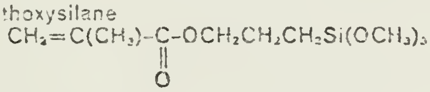
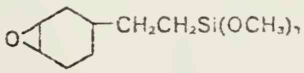
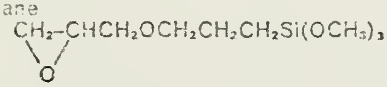
Subsequently, 29 is treated with divinyl sulfone (30) to form compound (31), which can be coupled to the amino groups of proteins or ligands.





Soybean trypsin inhibitor has been coupled to agarose by this method and trypsin has been purified on the resulting resin.

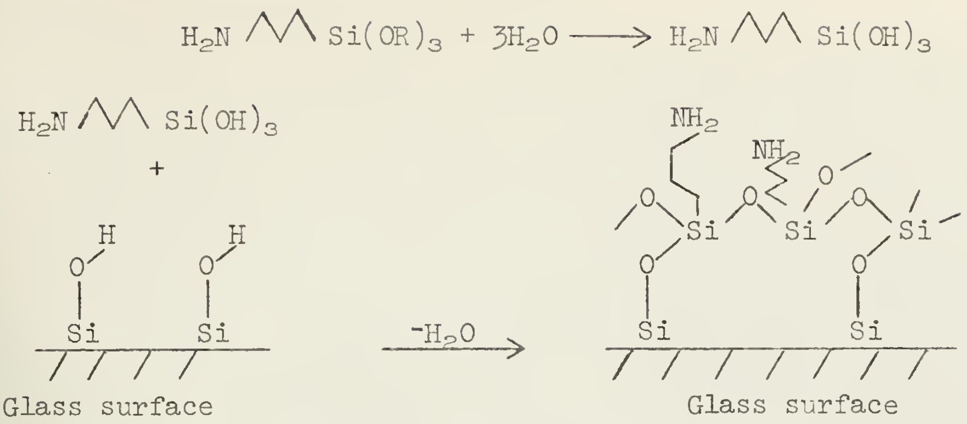
Table 1 Commercially available silane coupling reagents

Chemical name	Structure
Vinyltriethoxysilane	$CH_2{=}CHSi(OC_2H_5)_3$
Vinyltrimethoxysilane	$CH_2{=}CHSi(OCH_3)_3$
Vinyl-*tris*(β-methoxyethoxy)silane	$CH_2{=}CHSi(OCH_2CH_2OCH_3)_3$
γ-Methacryloxypropyltrimethoxysilane	 $CH_2{=}C(CH_3)\text{-}\underset{\underset{O}{\Vert}}{C}\text{-}OCH_2CH_2CH_2Si(OCH_3)_3$
β-(3, 4-Epoxycyclohexyl)-ethyltrimethoxysilane	
γ-Glycidoxypropyltrimethoxysilane	
Vinyltriacetoxysilane	$CH_2{=}CHSi(OOCCH_3)_3$
γ-Mercaptopropyltrimethoxysilane	$HSCH_2CH_2CH_2Si(OCH_3)_3$
γ-Aminopropyltriethoxysilane	$NH_2CH_2CH_2CH_2Si(OC_2H_5)_3$
N-β-(Aminoethyl)-γ-aminopropyltrimethoxysilane	$NH_2CH_2CH_2NHCH_2CH_2CH_2Si(OCH_3)_3$
γ-Chloropropyltrimethoxysilane	$ClCH_2CH_2CH_2Si(OCH_3)_3$

4. Porous glasses

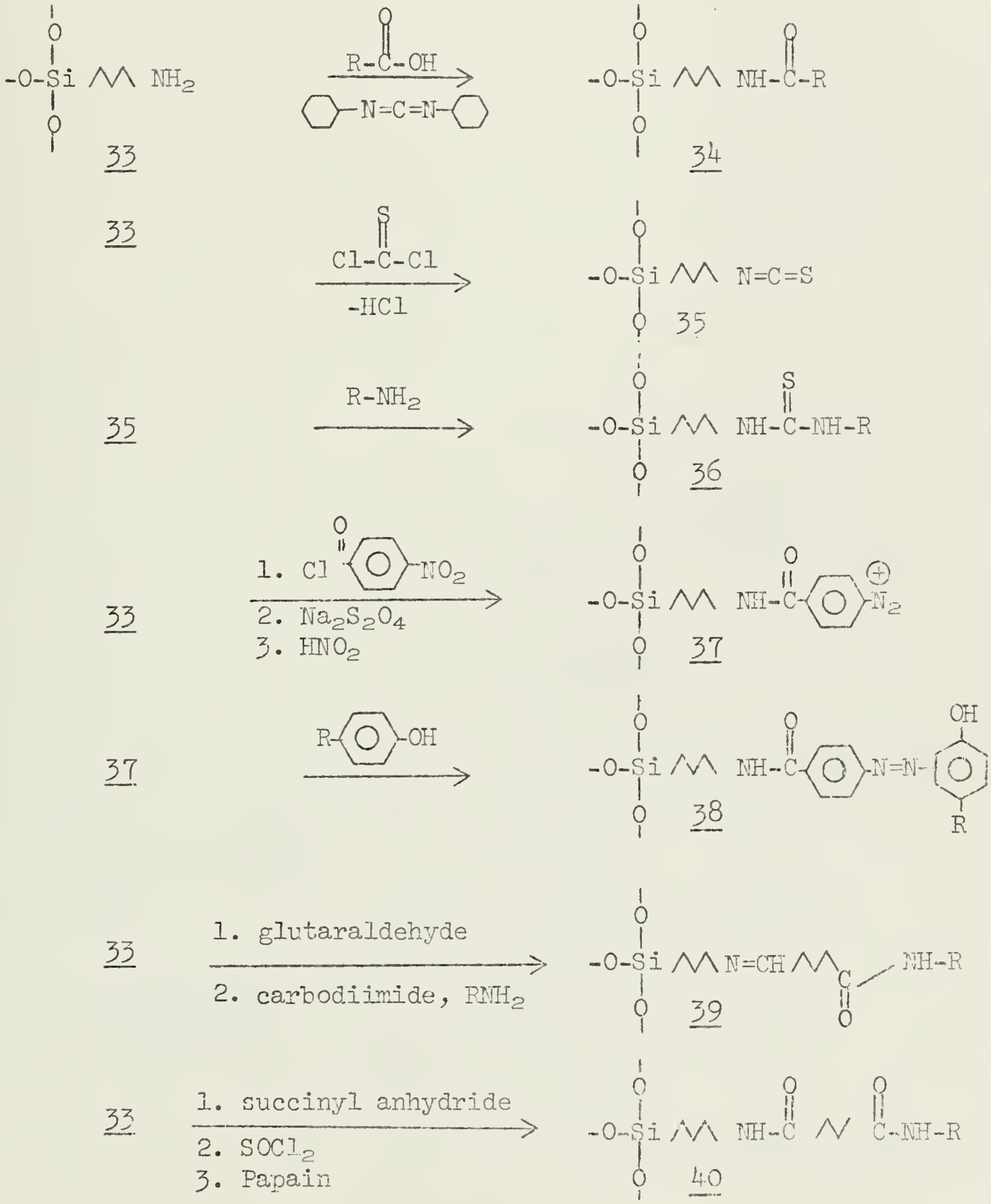
Porous glass beads, which have the advantage of being resistant to microbial attack, extreme pH and organic solvents, have been used recently as solid supports for affinity chromatography and enzyme immobilization. Although the silanyl hydroxyl groups on the glass surface are usually not reactive enough to couple with organic molecules, many silane coupling reagents have been devised and commercialized (Table 1).[24] The generalized reaction between the glass surface and the silane coupling reagents is shown in Scheme V.

Scheme V



Several ligands and enzymes have been coupled to porous glasses. The commonly employed coupling reaction is shown in Scheme VI.[25,26]

Scheme VI



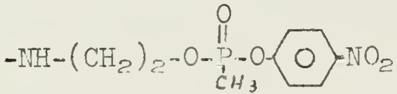
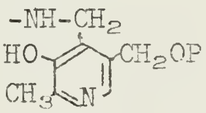
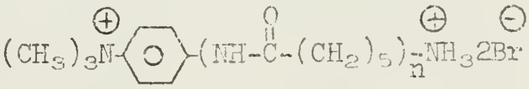
APPLICATIONS OF AFFINITY CHROMATOGRAPHY

The concept of affinity chromatography and enzyme immobilization has been used not only for the isolation and purification of proteins but also for many other biochemical studies. This seminar can not deal with these many aspects in detail. We will be concerned only with the application of affinity chromatography to protein purification. An excellent review on the applications of affinity chromatography and enzyme immobilization has been reported by Orth and Brühmer.[6]

The first purification of an enzyme by affinity chromatography dates back to 1910 when Starkenstein[27] observed the strong binding of amylase to insoluble starch. In 1933, Holmberg[28] reported the separation of α - and β- amylase by adsorption onto starch. The purification of enzymes by affinity chromatography was not widely used until the 1968 introduction of agarose as a solid support.[29] Currently, affinity chromatography is the most efficient and powerful method of protein purification. Many enzymes, for therapeutic use, must be highly purified prior to administration to humans to minimize immunological defense reactions. Affinity chromatography can help to achieve this goal. For example, human lysozyme has been purified in quantitative yield by this technique recently.[30]

A survey of recent applications (after 1972) of affinity chromatography to the purification of proteins is presented in Table 2. Affinity chromatography not only supplements conventional methods of purification but, in some cases, replaces older, tedious methods of protein purification.

Table 2 Isolation of Macromolecules by Affinity Chromatography

Proteins	Support	Ligand	Ref.
Soybean lipoxgenase	agarose	linoleic acid	31
Tetrahydrofolate dehydrogenase	"	methotrexate	32
aminoacyl-t-RNA synthetase	"	aminoacyl-t-RNA	33
acetylcholine esterase	"		34
β-galactosidase	"	p-aminophenyl-β-D-thiogalactopyranoside	35
Tyrosine amino transferase	"		36
IgA from human serum	"	goat IgG anti-human light chain	37
Protocollagen Proline hydroxylase (chick embryo)	"	reduced and carboxymethylated collagen	38
(liver) plasma membrane lipase	"	heparin	39
α - galactosidase	"	p-aminophenyl-melibioside	40
albumin	"	fatty acids	41
Nicotinate phosphoribosyl transferase (erythrocyte)	"	Nicotinate	42
antihemophilic factor (factor IV)	"	concanavalin A	43
Acetylcholine esterase	"	 n = 1, 2	44

c-AMP-dependent protein kinase	"	casein	45
ribonucleotide reductase	"	5'-deoxyadenosylcobalamin	46
δ - aminolevulinic acid synthetase	aminoethyl cellulose	Pyridoxamine-5-phosphate	47
leucocytes cell membrane receptors	agarose-BSA	Histamine	48
Acetylcholine Receptors	agarose	trimethylammonium bromide [N-(ε-aminohexanoyl)-3-aminopropyl]-hydrobromide	49
Carboxypeptidase A and B	"	arginine	50
penicillnase (B. Licheniformis)	"	cephalosporin C	51
Specific Coagulation factors IX XI	"	heparin	52
lipids, lipoproteins (from plasma)	"	Dodecylamine	53
Dihydroneopterin triphosphate synthetase	"	GTP	54
arylsulftase	"	psychosine sulfate	55
Thymidylate Synthetase (from L. Casei)	"	2-deoxy-uridylic acid	56
Methionyl-t-RNA synthetase (E. Coli)	"	methionine	57
phosphodiesterase (Bothrops atrox Venom)	"	O-(4-nitrophenyl)-C'-phenyl thiophosphate	58
Acetylcholine esterase (Bungarus fasciatus Venom)	"	Trimethyl-(m-aminophenyl)-ammoniumchloride hydrochloride	59
N-Acetyllactosamine Synthetase	"	N-acetylglucosamine	60
c-AMP dependent Diphosphoinositide kinase	"	c-AMP	61
Insulin receptor (liver cell)	"	insulin	62
RNA-dependent-DNA polymerase (from Rauscher Murine leukemia virus)	"	$(dT)_{12-18}$	63
"	"	antibody (antipolymerase)	64
Antibody to Morphine	"	succinyl-Morphine	65

REFERENCES

1. P. Cuatrecasas, J. Biol. Chem., 245, 3059 (1970).
2. P. Cuatrecasas and C. A. Anfinsen, Ann. Rev. Biochem., 753 (1971).
3. P. Cuatrecasas and C. A. Anfinsen, Methods in Enzymology, 31, 345 (1971).
4. P. Cuatrecasas, Adv. in Enzymology, 36, 29 (1972).
5. L. S. Lerman, Pro. Nat. Acad. Sci., USA, 39, 232 (1953).
6. H. D. Orth and W. Brühmer, Angew. Chem. Int. Ed., 11, 249 (1972).
7. H. H. Weetall, Sci., 166, 615 (1969).
8. H. H. Weetall and L. S. Hersh, Biochim. Biophys. Acta., 185, 464 (1969).
9. C. R. Lowe and P. D. G. Dean, FEBS Letters, 14, 313 (1971).
10. Zvi Er-el et al., Bioch. Biophys. Res. Com., 49, 383 (1972).

11. D. Campbell and A. Malley, J. Amer. Chem. Soc., 85, 487 (1963).
12. L. H. Kent and J. H. R. Slade, Biochem. J., 77, 12 (1960).
13. A. T. Jagendorf et al., Biochim. Biophys. Acta., 78, 516 (1963).
14. M. A. Mitz and L. J. Summaria, Nature, 189, 576 (1961).
15. P. T. Gilham, J. Amer. Chem. Soc., 84, 1311 (1962).
16. P. T. Gilham, ibid., 86, 9982 (1964).
17. P. T. Gilham, Biochem., 7, 2809 (1968).
19. J. Porath, R. Axén and S. Ernback, Nature, 215, 1491 (1967).
20. R. Axén, J. Porath and S. Ernback, Nature, 214, 1302 (1967).
21. R. Axén and S. Ernback, Europ. J. Biochem., 18, 351 (1971).
22. P. Cuatrecasas, Nature, 228, 1327 (1970).
23. J. Porath and L. Sundberg, Nature New Biol., 238, 261 (1973).
24. B. M. Cammeron and J. G. Marsden, Chem. Brit., p. 381 (1972).
25. H. H. Weetall, Res./Dev., p. 18 Dec. (1971).
26. H. H. Weetall and R. D. Mason, Biotech. Bioeng., 15, 455 (1973).
27. E. Starkenstein, Biochem. Z., 24, 210 (1910).
28. O. Holmberg, Biochem. Z. 258, 134 (1933).
29. P. Cuatrecasas, M. Wilchek and C. B. Anfinsen, Pro. Nat. Acad. Sci. USA, 61, 636 (1968).
30. C and EN, p. 15, Sept. 4, 1972.
31. S. Grossman, et al., Biochim. Biophys. Acta., 289, 77 (1972).
32. P. L. Chello et al., ibid., 268, 30 (1972).
33. S. Bartkowiak and J. Parvelkiewicz, ibid., 272, 137 (1972).
34. Y. Ashani and J. B. Wilson, ibid., 276, 317 (1972).
35. R. J. Robinson, P. Dunnill and M. D. Lilly, ibid., 285, 28 (1972).
36. J. V. Miller, P. Cuatrecasas and E. R. Thompson, ibid., 276, 407 (1972).
37. G. W. Litman and R. A. Good, ibid., 263, 89 (1972).
38. R. A. Bery and D. J. Prokop, J. Biol. Chem., 248, 1175 (1973).
39. G. Assmann et al., ibid., 248, 1992 (1973).
40. C. Mapes and C. Swerley, ibid., 248, 2461 (1973).
41. T. Peters, H. Toniuchi and C. Anfinsen, ibid., 248, 2447 (1973).
42. J. Niedel and L. S. Dietrich, ibid., 248, 350 (1973).
43. M. Legaz et al., ibid., 248, 3946 (1973).
44. T. L. Rosenberry et al., ibid., 247, 1555 (1972).
45. J. D. Corbin et al., ibid., 247, 3736 (1972).
46. R. H. Yamada and H. P. C. Hogenkamp, ibid., 247, 6266 (1972).
47. M. J. Whiting and W. H. Elliot, ibid., 247, 6818 (1972).
48. K. L. Melmon et al., Sci., 177, 707 (1972).
49. J. Schmidt and M. A. Raftery, Biochem., 12, 852 (1972).
50. B. J. Gates and J. Travis, Biochem., 12, 1867 (1973).
51. L. J. Crane, G. E. Bettinger and J. O. Lampen, Bioch. Bioph. Res. Com., 50, 220 (1973).
52. P. W. Gentry and B. Alexander, ibid., 50, 500 (1973).
53. D. G. Deutsch, et al., ibid., 50, 758 (1973).
54. R. J. Jackson, et al., ibid., 51, 428 (1973).
55. J. L. Breslow and H. R. Sloan, ibid., 46, 919 (1972).
56. P. V. Danenberg et al., ibid., 49, 1029 (1972).
57. M. Robert Gero and J. P. Waller, Europ. J. Biochem., 31, 315 (1972).
58. A. Frischauf and F. Eckstein, ibid., 32, 479 (1973).
59. V. Kumar and W. Elliot, ibid., 34, 586 (1973).
60. T. Helting and B. Erbing, Biochim. Biophys. Acta., 293, 94 (1973).
61. C. Torda, ibid., 286, 389 (1973).
62. P. Cuatrecasas, Proc. Nat. Acad. Sci., 69, 1277 (1972).
63. B. I. Gerwin et al., ibid., 69, 2599 (1972).
64. D. M. Livingston et al., ibid., 69, 393 (1972).
65. E. J. Simon, W. A. Dale and J. M. Miller, ibid., 69, 1835 (1972).

RECENT APPLICATIONS OF ALKALI METAL N,N-DIALKYLAMIDES

Reported by George Luteri November 12, 1973

Alkali metal amides are strong bases with pK values of ca. 35, which are intermediate between alkoxides and organometallic compounds.[1] Although it has been recognized for many years that the nucleophilic character of the amides could be controled by the choice of appropriate alkyl groups,[2] only relatively recently have researchers begun to take full advantage of this property. This seminar reviews some of the recent investigations into the use of alkali metal N,N-dialkylamides as non-nucleophilic strong bases.

PREPARATION OF ARYLCYCLOPROPANES

Arylcyclopropanes are usually synthesized by the reaction of olefins with phenyl carbenes or carbenoids[3] that are often generated by: a) photolysis[4] or zinc halide[5] induced decomposition of aryldiazomethanes; b) photolysis of stilbene oxides;[6] or c) reaction organolithium compounds with benzal bromides[3] or iodides.[7a] Benzal chlorides react with methyllithium or potassium tert-butoxide to give α-chlorocarbenes.[7b] Benzyl chlorides react with alkoxides,[8] triphenylmethides,[9] Grignards[10] and alkyllithium compounds[11] to give either nucleophilic displacement of chloride or metal-halogen exchange, they react with N,N-dialkylamides both by chloride displacement[12] to give amines and by α-proton abstraction[12,13] to give carbenoids.[5] The recent study by Olofson and Dougherty[13] has shown that benzyl chloride reacts with sterically hindered N,N-dialkylamides preferentially by α-proton abstraction, to give, in the presence of cyclohexene, 7-phenylnorcarane (1). The yields of 1 attained using lithium dicyclohexylamide (LiDCA) or lithium 2,2,6,6-tetramethyl piperidide (LiTMP) are comparable to the yields from the benzyl bromide method,[3] and although the yields are lower than with the zinc halide/aryldiazomethane method,[5] the benzyl chloride/amide method is more convenient and economical.

PREPARATION OF BENZYNES

One of the more popular techniques for generating benzynes is the dehydrohalogenation of arylhalides with strong bases such as organometallic compounds and substituted or unsubstituted metal amides. The former suffer the disadvantage of reacting with the resultant benzyne and are too efficient as matalating agents to allow a wide choice of substances to be reacted with the benzynes. The amides also are known to react nucleophilically with the benzynes, although less so than the organometallic bases, and can reduce the aryl halides.[14] Recently it has been demonstrated[13b,c] that sterically hindered dialkylamides having no α-hydrogens and which can not reduce aryl halides are much less prone to add to benzynes than are previously studied bases. For example, the system of o-chloroanisole, lithium dialkylamide, and lithium $C\equiv C$-ph in THF produced m-methoxytolan in less than 1% yield with $LiN(CH_3)_2$ but in greater than 80% yield with LiTMP.

REACTIONS WITH CARBONYL COMPOUNDS

Numerous studies have pointed out the inertness toward the carbonyl function of alkali metal N,N-dialkylamides in reactions involving proton abstraction from carbonyl compounds. In metalations of N,N-dialkylbenzene carboxamides,[15] lithium carboxylates,[16] polyketones[17] and in generation of ester[18] and amide[19] enolates, lithium diisopropylamide (LiDIA) was found superior to other metalating agents. Rathke[20] also reported the use of lithium bis(trimethylsilyl)amide (LiTMSA) and lithium isopropyl-cyclohexyl amide (LiPCA) to form ester enolates in near quantative yields. Borch[21] found that LiTMSA enabled unprecedented yields of greater that 90% in the Darzens condensation of simple aliphatic aldehydes. However, only a few systematic studies have been made comparing the various alkyl amides among themselves

and with other bases. Two early studies, one by Hauser and coworkers[22] using dialkylamino magnesium bromides and the other by Levine,[2] pointed out that in ester condensation reactions the yields of β-ketoesters tended to be greater, with less carboxamides as sideproducts, when sterically hindered amides were used. A recent reinvestigation by Olofson and Dougherty[13b,c] of ester condensations effected by numerous lithium dialkylamides, found good correlation between the yield of β-keto ester and the amount of steric hinderance of the dialkyl amide.

CONCLUSION

The potential utility of alkalimetal N,N-dialkyl amides as strong bases of controlable nucleophilicity has been demonstrated in the above discussion. Other applications of these bases such as the generation of polymerizable hydrocarbons[23] are under investigation. It is probably safe to predict that these compounds will find an important place among the reagents used in organic chemistry.

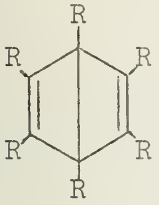
BIBLIOGRAPHY

1. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structures," McGraw-Hill Book Co., New York, N.Y., 1968, p. 219.
2. M. Hamell and R. Levin, J. Org. Chem., 15, 162 (1950).
3. W. Kirmse, "Carbene Chemistry," 2nd Ed., Academic Press, New York, N.Y., 1971.
4. G. L. Gloss and R. A. Moss, J. Amer. Chem. Soc., 86, 4042 (1964).
5. S. H. Goh, L. E. Class, and G. L. Closs, J. Org. Chem., 34, 25 (1969).
6. H. Kristinsson and G. W. Friffin, J. Amer. Chem. Soc., 88, 1579 (1966).
7. a) R. A. Moss, J. Org. Chem., 30, 3261 (1965); b) ibid., 27, 2683 (1962).
8. P. T. Lansbury and V. A. Pattison, ibid., 27, 1933 (1962); (J. F. Bunnett and J. D. Reinheimer, J. Amer. Chem. Soc., 84, 3284 (1962)); K. Kinder, Justus Liebigs. Ann. Chem., 452, 90 (1927).
9. P. T. Lansbury and R. Thedford, J. Org. Chem., 27, 2383 (1962).
10. H. Gilman and F. K. Cartledge, J. Organometal. Chem., 2, 447 (1964); R. West and W. H. Glaze, J. Chem. Phys., 34, 685 (1961).
11. M. S. Kharasch, W. Nudenberg and E. K. Fields, J. Amer. Chem Soc., 66, 1276 (1944).
12. C. Hauser. W. Brasen, P. Skell, S. Kantor and A. Brodhag, ibid., 78, 1653 (1955).
13. a) R Olofson and C Dougherty, ibid., 95, 581 (1973); b) ibid., 95, 582 (1973); c) C Dougherty, Ph D Thesis, The Pennsylvania State University, University Park, Pennsylvania, 1972.
14. R. W. Hoffman, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.
15. R. Ludt, J. Griffiths, K. McGrath and C. Hauser, J. Org. Chem., 38, 1668 (1973).
16. P. L. Creger, J. Amer. Chem. Soc., 89, 2500 (1967); ibid., 92, 1396,1397 (1970); J. Org. Chem., 37, 1907 (1972).
17. T. Howarth, G. Murphy and T. Harris, J. Amer. Chem. Soc., 91, 517 (1969); T. Harris and G. Murphy, ibid., 93, 6708 (1971).
18. S. Reiffers, H. Wynberg and J. Strating, Tetrahedeon. Lett., 3001, (1971).
19. T. Durst and M. LeBelle, Cov. J. Chem., 50, 3196 (1972).
20. a) M. Rathke, J. Amer. Chem. Soc., 92, 3222 (1970); b) M. Rathke and A. Lindert, ibid., 93, 2318 (1971).
21. R. Borch, Tetrahedron Lett., 3701 (1972).
22. C. Hauser and H. Walker, J. Amer. Chem. Soc., 69, 295 (1947); F. Frostick and C. Hauser, ibid., 71, 1350 (1949).
23. R. Eidenschink and T. Kauffmann, Angew. Chem., 84, 292 (1972).

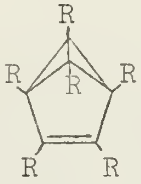
RECENT DEVELOPEMENTS IN THE CHEMISTRY OF BENZENE VALENCE BOND ISOMERS

Report by Gaylen R. Brubaker November 15, 1973

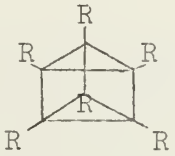
Although the structure of benzene has long since ceased to be controversial, recent photochemical studies have produced a scrambling of the carbon skeleton that requires the formation of nonplanar intermediates. This has stimulated interest in the nature of this scrambling and in the isolation of these intermediates and their derivatives. A review of valence bond isomers of substitued benzenes[1] and other aromatic systems[2] appeared in 1965. Because a more recent review of $(CH)_n$ rearrangements[3] surveys a portion of the subsequent work, this seminar will concentrate on post 1965 work related to the synthesis and reactions of benzvalene (tricyclo[3.1.0.0^{2,6}]hex-3-ene), Dewar benzene (bicyclo[2.2.0]hexa-2,5-diene), prismane (tetracyclo[2.2.0.0^{2,6}.0^{3,5}] hexane) and their hexamethyl derivatives. Photochemical discussions will be limited to isomerizations at 2537 Å.



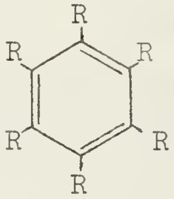
1



2



3



4

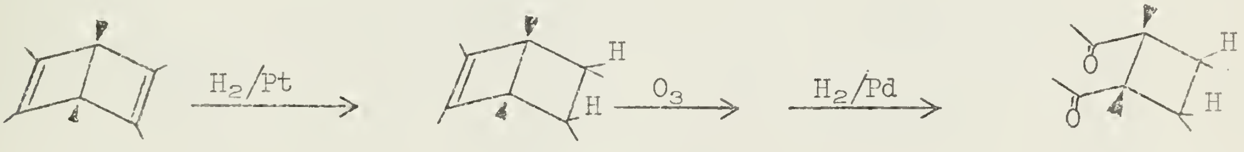
a R = H

b R = CH_3

Over the last decade, the photoylsis of benzene derivatives at 2537 Å have produced an extensive list of carbon skeletal rearrangements. Examples vary from the isomerization of methylbiphenyls[4,5] to the less sterically influenced isomerization of benzene-1,3,5-d_3 to benzene-1,2,4-d_3.[6] The study of 1,3,5-trimethylbenzene-1,3,5-C^{14} reveals that isomerization to 1,2,4-trimethylbenzene-1,2,4-C^{14} does in fact occur via skeletal transformation and not by substituent migration.[7] The use of t-butyl substituents has yielded an increase in steric interactions, as 1,2,4,5-tetra-t-butylbenzene has been shown to form 1,2,3,5-tetramethyl-t-butylbenzene.[8] This data is the basis for the contention that the isomerization occurs within the carbon skeleton and is not the result of steric interaction.

SYNTHESIS

Several derivatives of Dewar benzene have been synthesized from acetylenes by various additions to stabilized cyclobutadiene. This approach was extended to hexamethyl Dewar benzene (1b) via $AlCl_3$ trimerization of 2-butyne at or below 35° C; isomerization to hexamethylbenzene predominates above 50° C. The isolated product, 1b, is obtained in 60-70% yield and is stable at low temperatures, having a half-life of 105 hr at 120° C.[9] Characterization by nmr reveals singlets at δ1.55 and δ1.05 (2:1); IR and UV are consistent with a nonconjugated system.[9,10] Hydrogenation of 1b yields hexamethyl bicyclo[2.2.0]hex-3-ene (5), which can be converted to 1,2,3,4-tetramethyl-1,2-acetylcyclobutane (6).[10]



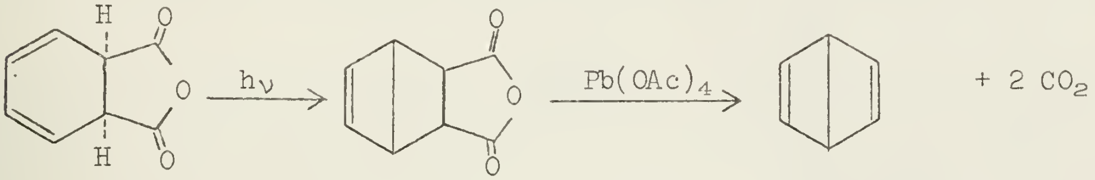
1b

5

6

Dewar benzene (1a) has been synthesized by van Tamelen as described in Scheme 1. The anhydride 7 was characterized by spectral and degradative means prior to reaction. The nmr of 1a consists of two multiplets; a triplet at δ6.55 and a quintet at δ3.84 in a 2:1 ratio; UV shows only end absorbtion. Hydrogenation with H_2N_2 yields bicyclo[2.2.0]hexane which was compared with an authentic sample.

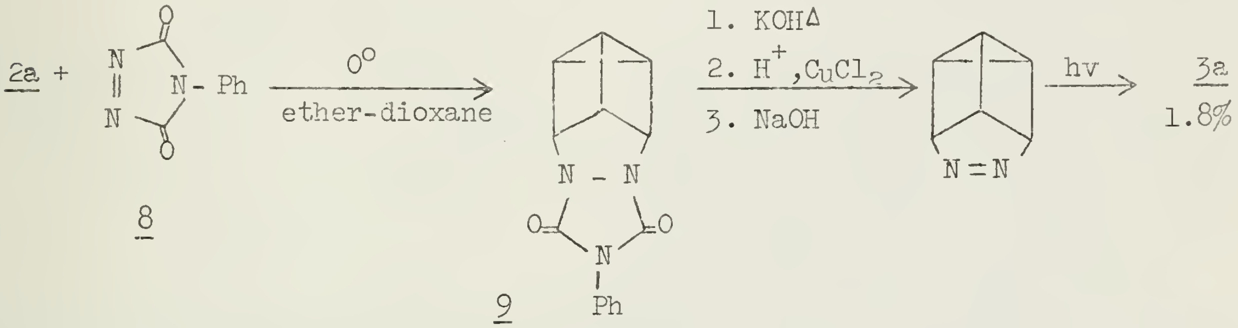
Scheme 1



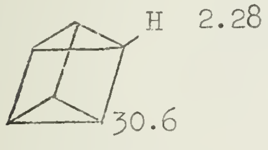
7   20% 1a

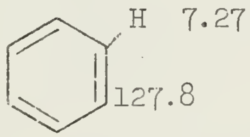
Photoylsis of 1b at 2537 Å in butane has been shown to form hexamethylprismane 3b, which can further isomerize to hexamethylbenzene (4b). Isolation of 3b yields a solid, mp 89-90.5°, with a single nmr absorbtion at δ0.97 and UV absorbtion $\epsilon_{230}=990$, $\epsilon_{250}=139$, $\epsilon_{270}=33$.[12] The half life of 3b is 2 hr at 100° inspite of the fact that isomerization is exothermic by 90 Kcal/mole. This is a powerful example of chemical inertness explained by orbital symmetry selection rules.[13]

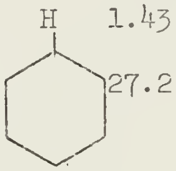
Early this year, Katz and Acton reported the first synthesis of unsubstitued prismane 3a. Benzvalene (2a) was treated with 4-phenyltriazolinedione (8) to form precursor 9, which was hydrolysed and oxidized to axoprecursor 10. Irradiation at 30° gives the desired product 3a in 1.8% isolated yield.



Structure proof includes the nmr data listed, as well as mass spectral and UV data consistent with the assigned structure.[14] The half life of 3a at 90°





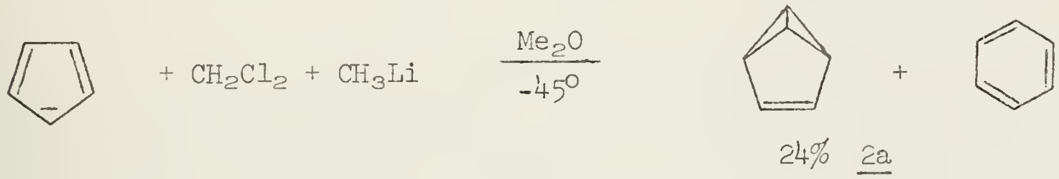


$J_{C_{13}H}$ = 180 Hz

3a   4a

is 11 hr, but it is considered stable at room temperature. Early attempts at similar schemes failed when the final irradiation was performed at other temperatures, higher temperatures yield rearranged products and lower temperatures give rearranged diazocompounds.[15]

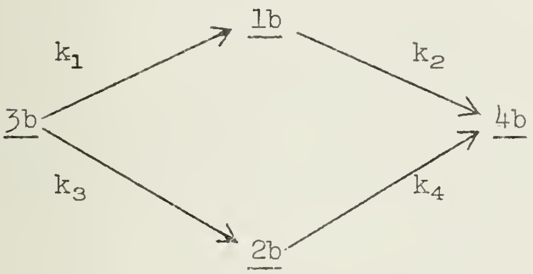
Hexamethylbenzvalene (2b) has been isolated only as an intermediate in the photochemical conversion of 3b to 4b. The data reported indicates nmr absorbtion at δ1.025, δ0.95 and δ0.83 with equal intensities. The unsubstituted 2a has recently been synthesized via the reaction of cyclopentadieneyl anion and methylene chloride in the presence of strong base. The product was found stable in solution but explosive to contact

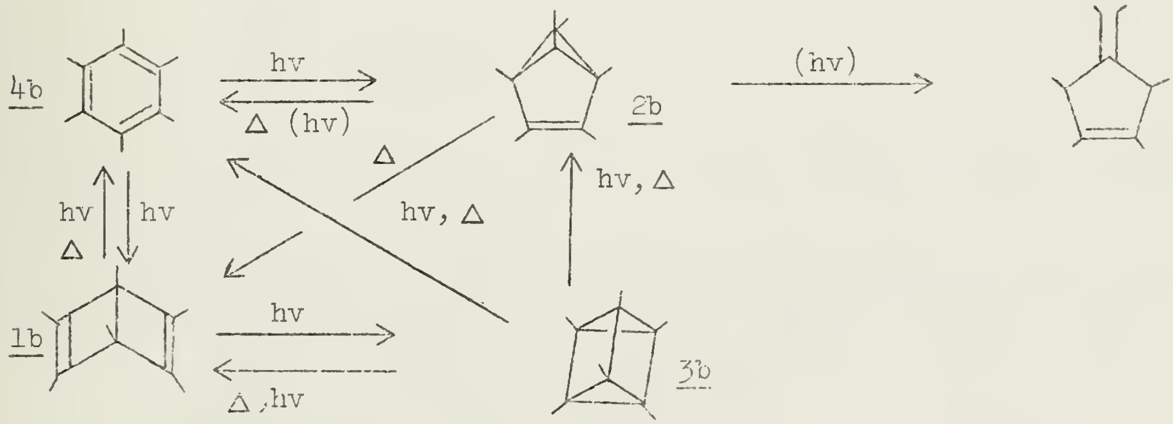


as a neat liquid. The nmr shows three equally intense peaks which have been assigned as follows; $H_{3,4}$, δ5.95 (unsym triplet, J=1.5, 1.7); $H_{1,6}$ δ3.55 (sym triplet J=1.5); $H_{2,5}$, δ1.85 (quintet, J_{Tot}=6.2). This assignment is supported by the collapse of both triplets to singlets upon irradiation at δ1.85.[16] Microwave analysis shows a dihedral angle of 106.0± 0.03° and C-C sigma bond lengths of 1.452 to 1.529Å.[17]

REACTIONS

The first isolation of compounds of type 1, 2, and 3 were from the photolysis of benzene and its derivatives at 2537Å. These reactions have limited synthetic value since many isomers themselves absorb at this wavelength and thus are formed in steady state concentrations only. Irradiation of 1b at 3° for 170 hr yields 4b (15%), 3b (5%) and starting material, but some 4b is presumably a result of the 3b pathway. The thermal conversion of 3b has also been studied, and reveals two parallel path to the final product, 4b, where $k_1 > k_2$ and $k_4 > k_3$.[13] Benzvalene has been shown to isomerize to 4b and fulvene upon irradiation,[19] but fulvene will not isomerize to any of the other isomers. Combining the above information, we infer the following reaction scheme, where parenthesis indicate conversions observed only for unsubstituted compounds.[19] Most of these pathways are known for a variety of other derivatives as well.[3]



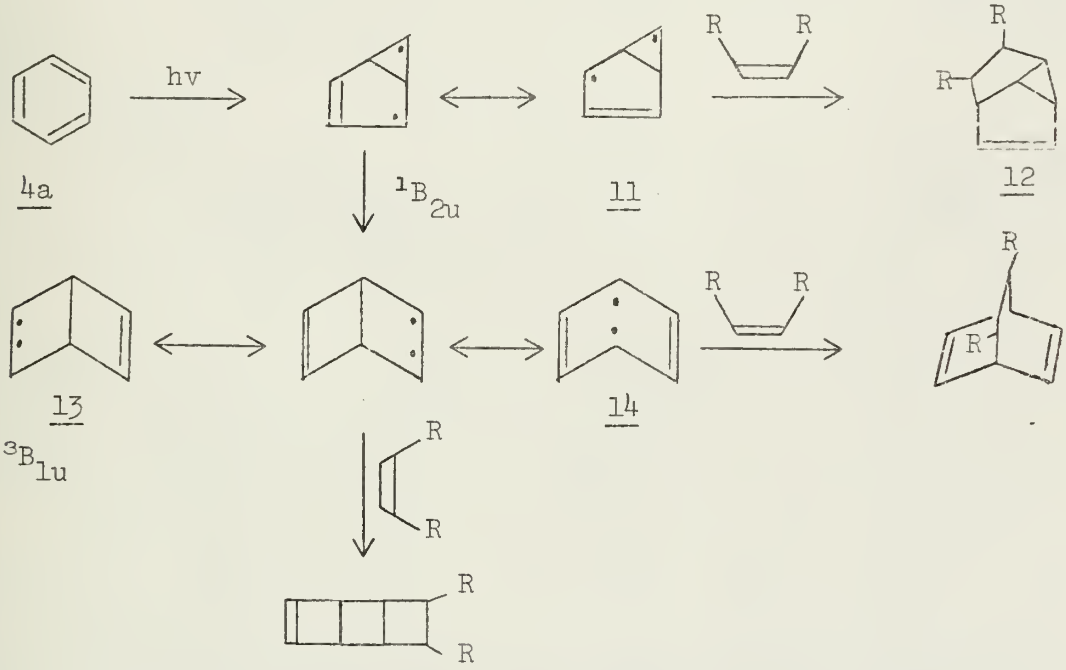


These findings have stimulated a variety of articles related to the molecular orbital[20-24], orbital symmetry[25-29] and photochemical[30-36] implications of these conversions. Differential scanning calorimetry has been used as a basis for determining the $\Delta H_{isomerization}$, activation energy and angle strains for the hexamethyl derivatives. The angle strain of 1b is found to be 44.5 Kcal/mole compared to 116 Kcal/mole for 3b. This is in good agreement with a value of 107 Kcal/mole which is twice the sum of the strain energy of cyclopropane and cyclobutane.[37] Orbital symmetry rules prohibit interconversions along the described pathways, from the ground state[29], consistent with the large activation energies observed. A few attempts have been made to postulate twisted[29] or Mobius[27] transition states, but these are as yet based only on theoretical considerations.

isomerization	ΔH	E_a Kcal/mole
3b → 4b	-91.2	
1b → 4b	-59.5	37.2
3b → 1b	-31.7 (by diff)	33.8

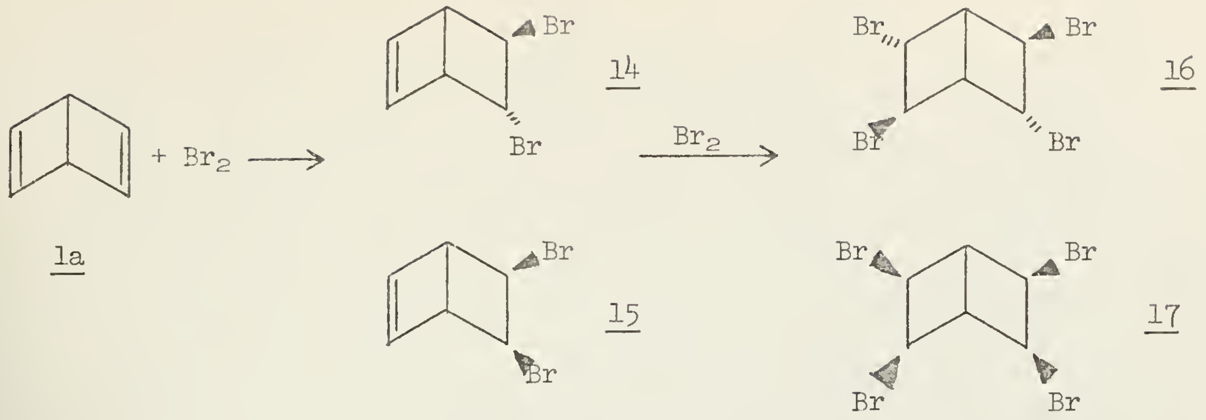
The photochemical mechanisms have been studied over a longer period of time than the thermal, and support the initial formation of a singlet state $(^1B_{2u})$ which can either crossover to a triplet state $(^3B_{1u})$, fluoresce, or react. The triplet state is then converted to a valence bond isomer, destroyed by collision, or allowed to cross back to a high vibrational level of the benzene ground state.[31]

Scheme 2



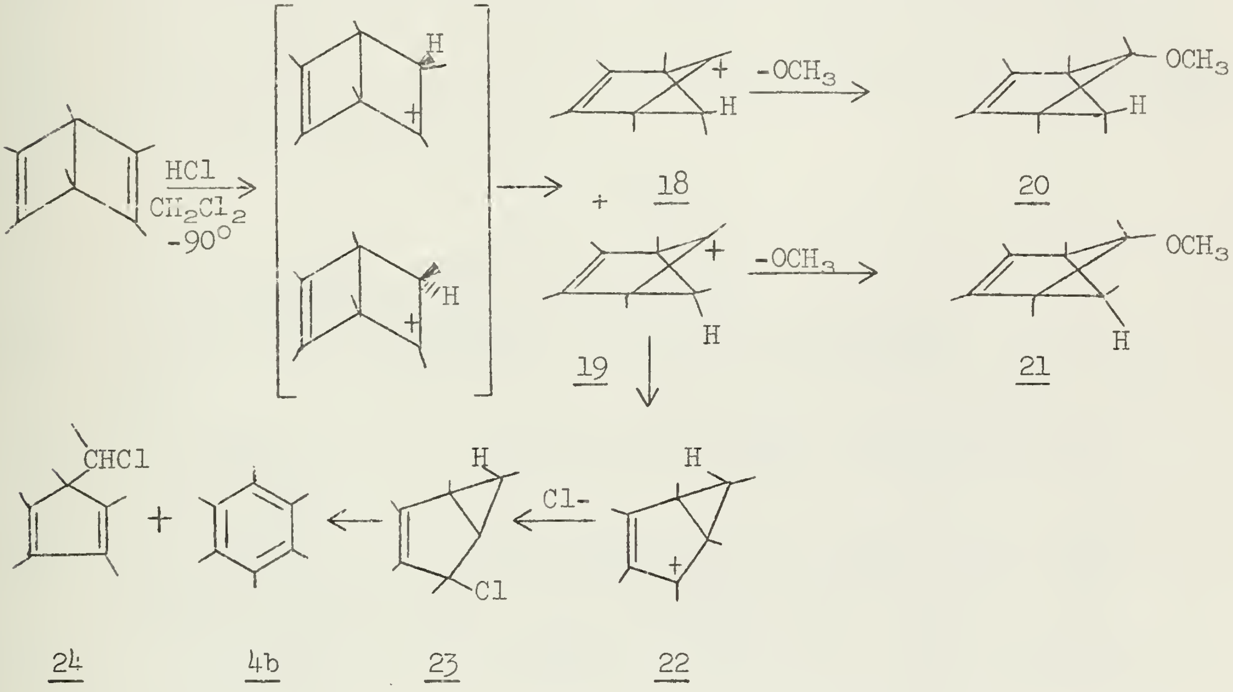
The transformations outlined in scheme 2 have been suggested as one pathway which is consistent with observed products and the symmetry requirements of the electronic transitions.[34]

The developement of nonphotochemical synthesis of hexamethyl Dewarbenzene and benzvalene has led to the examination of ionic and concerted olefinic reactions in these strained systems[37-48] as well as cataylitic ring openings leading to a variety of trapped intermediates.[16,49-57] Concerted attacks on 1b have been predominately from the less hindered exo side, and include hydrogenation,[45] epoxide formation,[39,51] the addition of phenylazide[41,43,58] and diphenylazocarbene[39]. The diol formation by OsC_4 has resulted in formation of cis-endo product[42], while bromination gives predominately trans addition with no cis-endo product. The addition of one



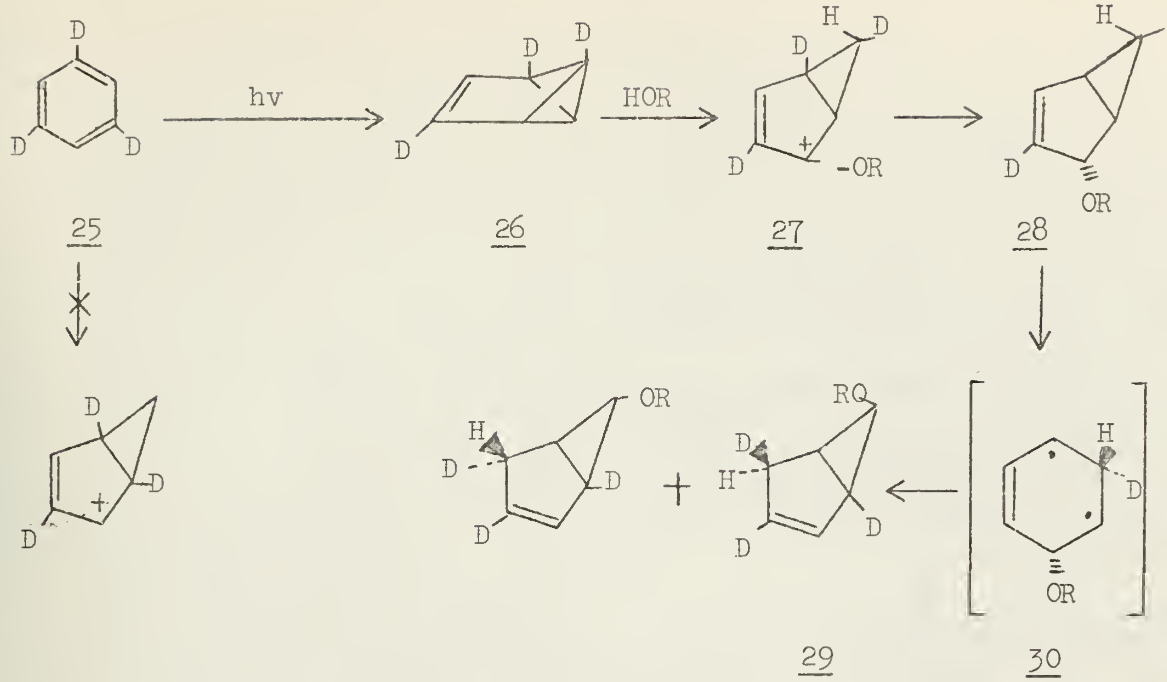
mole of bromine yields a 70:30 mixture of dibromides 14 and 15, while the tetrabromoproduct has been identified as 95% trans-anti-trans-2,3,5,6-tetrabromobicyclo[2.2.0]hexane (16) by nmr and X-ray analysis. The cis-17 compound was the only other product isolated, others were detected however.[48]

The treatment of 1b with HCl under a variety of concentrations and temperatures, indicates that although exo attack may give the thermodynamically most stable intermediate, in some cases endo attack is kinetically favored. The initial protonation is performed at -100° c and is observed by nmr to



afford >80% endo attack to form cation 19 if chloride ion concentration is low. Raising the temperature to -50° results in the establishment of thermodynamic equilibrium, a 3:1 mixture of 18 and 19. Further heating allows rearrangement to the allylic cation 22 which is trapped as the chloride but decomposes on standing to 24 and 4b.[53] This type of rearrangement (19-22) has also been observed in the hydrolysis of epoxides[51] and in the reaction of 1b with $Hg(OAc)_2$ and subsequent hydrolysis.[53]

Recent work with labeled benzvalene has produced similar findings. By labeling the C-2 position with deuterium, it was found that the C-2 and C-4 positions scramble much faster than the other positions. Benzene-1,3,5-d_3(25) was then used to show that the bicyclo[3.1.0]hex-3-en-2-yl cation (27) is formed via a benzvalene derivative, in contrast to a direct



formation of the cyclopropyl moiety. In comparing a series of reactions using different R groups, it appears that increased acidity of ROH results in a longer lifetime for the free ion 27 and a higher percent exo product 28. It was also found that the formation of 29 from 28 occurs with retention of steriochemistry with respect to the six membered ring, implying a planar transition state similar to 30.[40,41]

BIBLIOGRAPHY

1. H. G. Viehe, Angew. Chem., Int. Ed. Engl., 4, 746 (1965).
2. E. E. van Tamelen, ibid., 4, 738 (1965).
3. L. T. Scott and M. Jones Jr., Chem. Rev., 181 (1972).
4. U. Mende, J. L. Laseter and G. W. Griffin, Tetrahedron Lett., 3747 (1970).
5. R. A. Abramovitch and T. Takaya, Chem. Comm., 1369 (1969).
6. K. E. Wilzbach, A. L. Harkness and L. Kaplan, J. Amer. Chem. Soc., 90, 1116 (1968).
7. K. E. Wilzbach and L. Kaplan, ibid., 87, 4004 (1965).
8. E. M. Arnett and J. M. Bollinger, Tetrahedron Lett., 3803 (1964).
9. W. Schafer, Angew. Chem., Int. Ed. Engl., 5, 669 (1966).
10. W. Schafer and H. Hellman, ibid., 6, 518 (1967).
11. E. E. van Tamelen, S. P. Pappas and K. L. Kirk, J. Amer. Chem. Soc., 93, 6092 (1971).
12. D. M. Lemal and J. P. Lokensgard, ibid., 88, 5934 (1966).
13. J. F. M. Oth, Angew. Chem., Int. Ed. Engl., 7, 646 (1968).
14. T. J. Katz and N. Acton, J. Amer. Chem. Soc., 95, 2738 (1973).
15. B. M. Trost and R. M. Cory, ibid., 93, 5573 (1971).
16. T. J. Katz, E. J. Wang and N. Acton, ibid., 93, 3782 (1971).
17. R. D. Suenram and M. D. Harmony, ibid., 95, 4506 (1973).
18. W. Schafer, R. Criegee, R. Askani and H. Gruner, Angew. Chem., Int. Ed. Engl., 6, 78 (1967).
19. L. Kaplan and K. E. Wilzbach, J. Amer. Chem. Soc., 90, 3291 (1968).
20. K. Fukui, Tetrahedron Lett., 2009 (1965).
21. K. Fukui, Bull. Chem. Soc. Jap., 39, 498 (1966).
22. M. J. S. Dewar, Tetra. Supp., 8, 75 (1967).
23. M. Randic and Z. Majerski, J. Chem. Soc., 1289 (1968).

24. N. C. Baird and M. J. S. Dewar, ibid., 91, 352 (1969).
25. H. C. Longuet-Higgins and E. W. Abrahamson, ibid., 87, 2045 (1965).
26. E. Farenhorst, Tetrahedron Lett., 6465 (1966).
27. H. E. Zimmerman, J. Amer. Chem. Soc., 88, 1564, 1566 (1966).
28. R. Hoffman and R. B. Woodward, Acc. Chem. Res. 1, 17 (1968).
29. R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1971.
30. W. A. Noyles Jr. and D. A. Harter, J. Chem. Phys., 46, 674 (1967).
31. W. A. Noyles Jr., J. Amer. Chem. Soc. 84, 1502 (1962).
32. J. K. Foote, M. H. Mallone and J. N. Pitts Jr., ibid., 88, 3698 (1966).
33. P. J. Wagner, ibid., 89, 2820 (1967).
34. D. Bryce-Smith and H. C. Longuet-Higgins, Chem. Comm., 593 (1966).
35. I. Haller, J. Chem. Phys., 47, 1117 (1967).
36. G. H. Atkinson and C. S. Parmeter, J. Phy. Chem., 75, 1564 (1971).
37. J. F. M. Oth, Recl. Trav. Chim. Pays-Bas, 87, 1185 (1969).
38. E. E. van Tamelen and D. Carty, J. Amer. Chem. Soc., 89, 3922 (1967).
39. ibid., 93, 6102 (1971).
40. R. Srinivasan, ibid., 93, 3555 (1971).
41. L. A. Paquette, R. S. Haluska, M. R. Short, L. K. Reed and J. Clardy, ibid., 94, 529 (1972).
42. G. R. Krow and J. Reilly, Tetrahedron Lett., 3133 (1972).
43. L. A Paquette, S. A. Long Jr., M. R. Short, B. Parkinson and J. Clardy, ibid., 3141 (1972).
44. H. Vogeveen and D. W. Kwant, ibid., 3197 (1972).
45. H. C. Volger and H. Hogeveen, Recl. Trav. Chim. Pays-Bas, 86, 1356 (1967).
46. ibid., 88, 353 (1969).
47. H. van Bekkam, F. van Rantwijk, G. van Minnen-Pathus, J. D. Remininse and A van Veen, ibid., 88, 911 (1969).
48. L. A. Paquette and G. R. Krow, Tetrahedron Lett., 2139 (1968).
49. K. E. Wilzbach and L. Kaplan, J. Amer. Chem. Soc., 88, 2066 (1966).
50. L. Kaplan, J. S. Richer and K. E. Wilzbach, ibid., 2881 (1966).
51. ibid., 89, 1031 (1967).
52. A. Berson and N. M. Hasty Jr., ibid., 93, 1549 (1971).
53. D. J. Rausch and K. E. Wilzbach, ibid., 94, 8638 (1972).
54. D. Bryce-Smith, A. Gilbert and B. H. Orger, Chem. Comm., 512 (1966).
55. D. Bryce-Smith, A. Gilbert and H. C. Longuet-Higgins, ibid., 240 (1967).
56. H. Hogeveen and H. C. Volger, ibid., 1133 (1967).
57. G. Cueille and R. Fraisse Jullien, Tetrahedron, 28, 1331 (1972).
58. L. A. Paquette, S. A. Lang Jr., S. K. Porter and J. Clardy, Tetrahedron Lett., 3137 (1972).

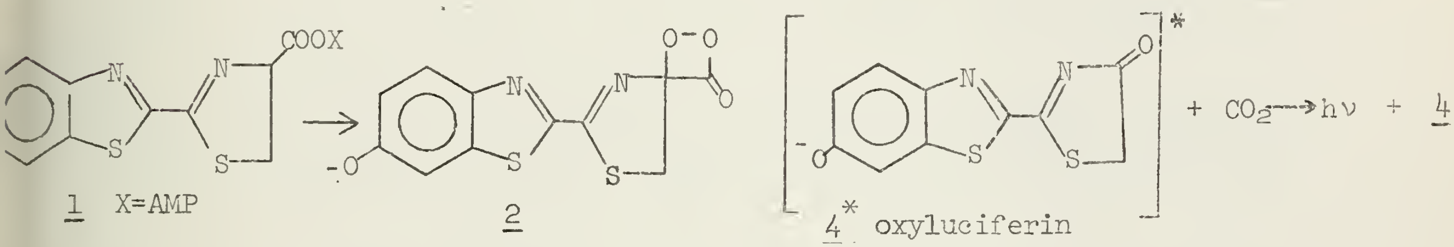
SOME RECENT STUDIES OF ORGANIC CHEMILUMINESCENT SYSTEMS

Reported by E. Robert Fretz November 19, 1973

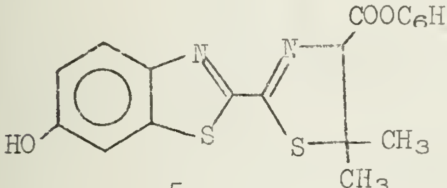
The first relatively simple chemical system recognized to be chemiluminescent was the lophine system studied by Radziszewski in 1877.[1] Since that time, a deluge of papers has appeared dealing with various chemiluminescent systems. Many excellent reviews[2] have recently appeared which cover the literature adequately through 1969. Since no reviews covering this subject have appeared since 1970, it is the purpose of this abstract to survey recent advances in organic chemiluminescent systems studied since 1969.

Although a number of biological systems have been studied for quite some time, several recent advances have been made in our understanding of these systems. The reactions of the American firefly luciferin is probably the best known of these systems. Studies of this system have been reviewed,[2a,g,f,e] and the mechanism proposed for the bioluminescence is shown in Scheme I.

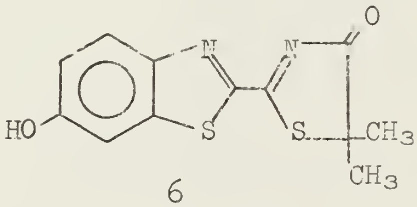
Scheme I



The luciferyl adenylate 1 is bioluminescent upon enzymatic oxidation by luciferase and chemiluminescent in basic dimethylsulfoxide (DMSO) solution.[3] The luciferin 1, when treated with small amounts of potassium *tert*-butoxide



5

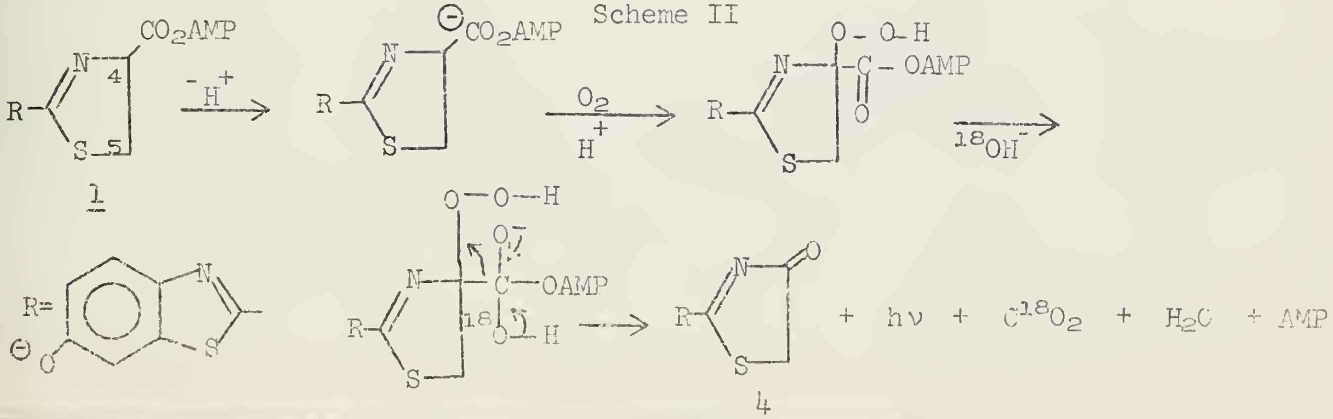


6

(*t*-BuOK) in DMSO[3c] produces red light (630nm). However, large amounts of base yield a yellow-green emission (555nm). This is similiar to the light emission of the enzyme catalyzed system at different pH values.[4] However, when the dimethyl luciferin derivative 5 is treated with base in DMSO, only the red emission is produced, suggesting that the dianion of 4 is involved in the yellow-green emission.

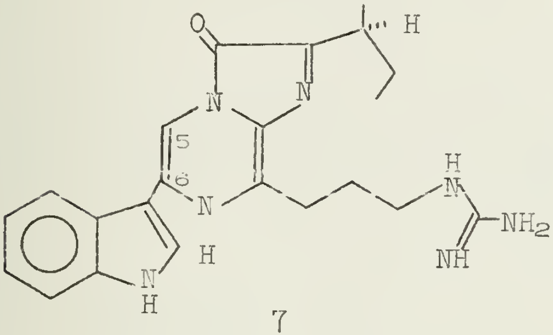
Recent results by DeLuca and Dempsey[5] contradict the proposed mechanism in Scheme I. According to Scheme I, one oxygen in the liberated CO_2 must come from oxygen (O_2). By using $^{18}O_2$ and $H_2{}^{18}O$ and an excess of luciferase at pH=7.8, it was found that one oxygen from H_2O is incorporated into CO_2 and that oxygen from O_2 is not incorporated into CO_2. The mechanism proposed by DeLuca and Dempsey is shown in Scheme II. A slower rate for this reaction is found if deuterium is substituted for hydrogen at C-4.[5]

Scheme II

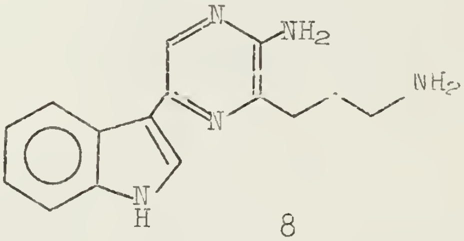


The dimethyl oxyluciferin 6 was isolated from reaction of 5 with guanidine carbonate in DMSO and its fluorescence spectrum matches the chemiluminescence spectrum for this reaction. Isolation of oxyluciferin 4 from reaction of luciferin 1 was unsuccessful,[6] with three other products being isolated instead. These same three colored products were also isolated from attempted synthesis of 4 by condensation of ethyl thioglycolate and 2-cyano-6-hydroxybenzothiazole. This reaction has recently been re-investigated.[7] By excluding oxygen and carrying out the reaction in methanol for two minutes at 0°C. oxyluciferin 4 was indeed obtained and characterized. By nmr, 4 was shown to exist in an enol form. Further, the fluorescence spectrum (λ_{max} = 556nm) in DMSO and guanidine carbonate under vaccuum is identical with the chemiluminescence spectrum of luciferin 1, supporting the assignment of the dianion of 4 as the emitter of the yellow-green light. Added oxygen changes the fluorescence spectrum to 498nm. Oxyluciferin 4 was also recently reported to have been isolated from chemiluminescence or *in vivo* firefly bioluminescence.[8] Comparison with synthetic samples shows oxyluciferin 4 to be the product of these reactions.

Another biologically important luminescent compound is the Cypridina hilgendorfii luciferin, the study of which has been reviewed.[9] Structure 7 has been proposed for this luciferin.[10] The position of the indol-3-yl moiety from this data as well as from an early complete synthesis of 7[11]



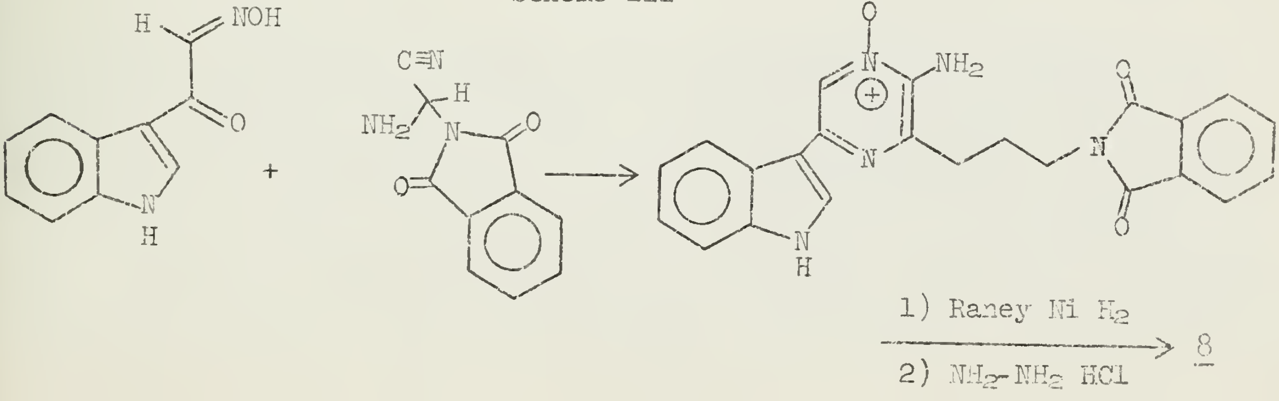
7



8

could be at either position 5 or 6. Cypridina etioluciferamine 8, a degradation product of luciferin 7, has been recently synthesized[12] in a manner which removes the ambiguity in assigning the position of the indol-3-yl group. This etioluciferamine 8 has been converted to luciferin 7 in two steps.[13] The synthesis of 8 is shown in Scheme III. On comparison, product 8 and natural Cypridina etioluciferin were found to be identical. An analog of luciferin 7 has recently been synthesized via another route by McCapra and Roth.[14] The native luciferin is thought to arise from trypotophan, isolucene and arginine. Luciferin 7 shows chemiluminescence in aprotic solvents. The mechanism[15] for this involves a one electron transfer from O_2 to

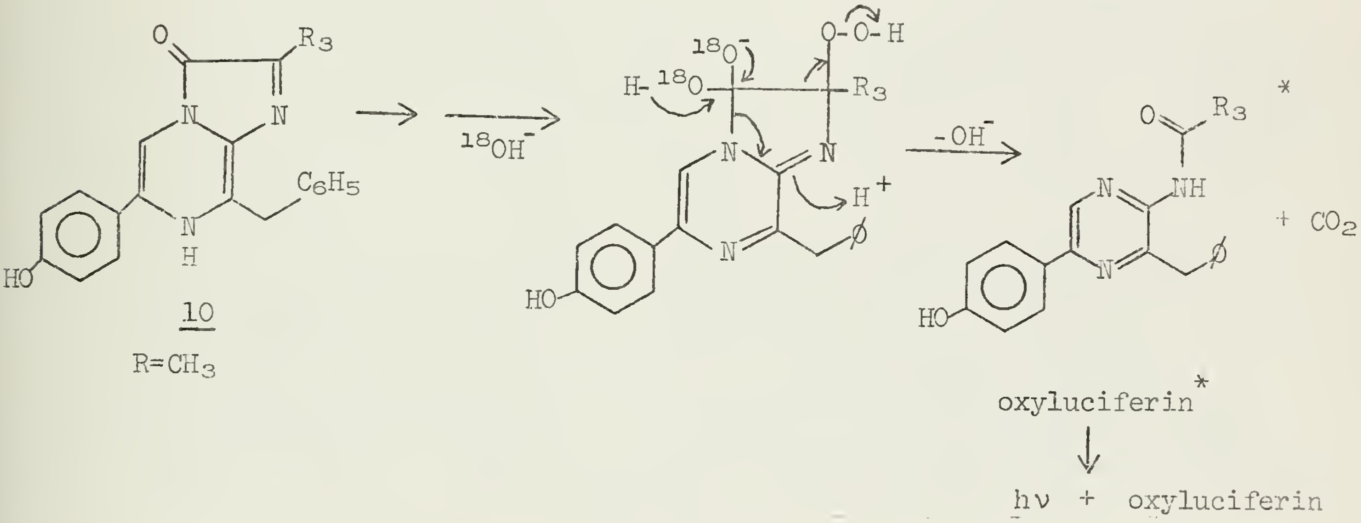
Scheme III



the luciferin anion producing a radical pair which combines to give the corresponding hydroperoxide anion which presumably decomposes through a dioxetane intermediate giving an acylaminopyrazine anion in a singlet excited state. While the three groups on the 3,7-dehydroimidazo [1,2-a] pyrazine nucleas are important in the bioluminescence of this luciferin, they are not necessary for the chemiluminescence.[16]

Other biological systems recently studied include the jellyfish aequorea luciferin 9 and Renilla reniformis (sea pansey) luciferin 10. Luciferin 9, called AF-350, was isolated from the photoprotein of the jellyfish and has been synthesized,[17] in a manner analogous to the synthesis of 8 shown in Scheme III. The synthetic luciferin has been found identical to the natural product. Recent studies on the mechanism of the jellyfish aequorea bioluminescence[18] indicate that AF-350 9 is not the actual light emitter. Instead a substituted AF-350 in which the primary amino group is converted into the p-hydroxyphenylacetamido moiety is thought to be the emitter. This substituted luciferin was isolated from the protein of the Jellyfish and has been shown to be the light emitter. The Renilla luciferin 10 has been synthesized from 9 by reaction with methyl glyoxal and acid.[19] The R group of the natural occuring luciferin is not methyl but is as yet an unknown complex functionality. However, synthetic 10 has been found to be biologically active with Renilla luciferase, and although only 10% as much light is produced, the fluorescence spectra of the synthetic and natural materials are identical. The mechanism for bioluminescence of luciferin 10 has been studied by DeLuca and coworkers[20] by use of $H_2{}^{18}O$ and $^{18}O_2$ labeled systems. Their results indicate that the oxygen in the CO_2 produced, comes from H_2O and not O_2, similar to the case of the firefly luciferin. Their proposed mechanism, shown in Scheme IV, does not indicate the formation of a dioxetane ring.

Scheme IV



10

R=CH_3

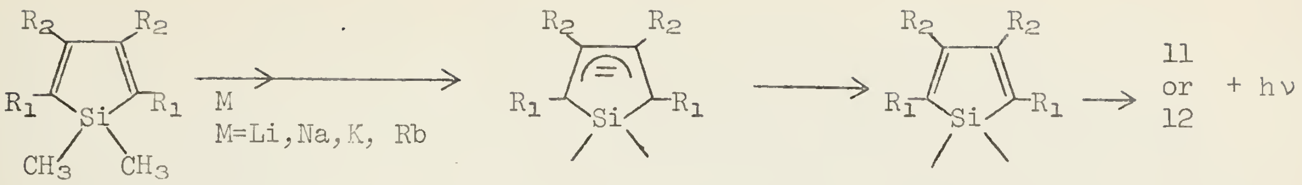
oxyluciferin*

↓

hν + oxyluciferin

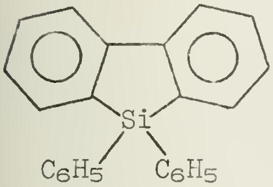
Phenyl substituted siloles, studied by E. Janzen and co-workers[21] have been reduced by alkali metals producing both the radical anions and dianions of the parent compounds. These dianions, on exposure to air, were found to produce a blue flash of light. It was found that 1,1-dimethyl-2,5-diphenylsilole 11 and 1,1-dimethyl-2,3,4,5-tetraphenylsilole 12 could be reduced to the corresponding dianions by lithium, sodium, and potassium, and on exposure to air, the parent siloles were produced quantitatively along with the blue light. Use of benzoyl peroxide gave nearly 10^3 times as much light as air oxidation. The fluorescence spectra of the siloles match the chemiluminescence spectra of the dianions and the scheme shown in Scheme V was proposed . It was assumed that the dianion is oxidized first to the radical anion whose further oxidation to

Scheme V

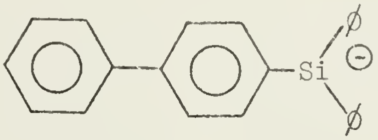


11 R$_1$=C$_6$H$_5$; R$_2$=H
12 R$_1$=R$_2$=C$_6$H$_5$

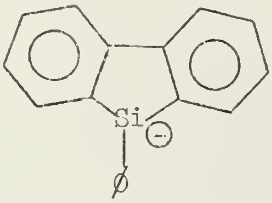
the silole is chemiluminescent. Potassium permanganate in THF and "moist oxygen" were also used as oxidants. Analogous results were obtained with the corresponding phospholes although benzoyl peroxide is necessary to oxidize the dianions produced. When 1,2,3,4-tetraphenyl thiophene-S-dioxide is reduced to the dianion and air oxidized, light of different wavelength than the fluorescence spectrum of the parent compound is produced. Polycyclic organosilane 13 can be reduced to the corresponding radical anion. Further reduction is followed by loss of a phenyl group which forms a biphenyl radical anion



13



14

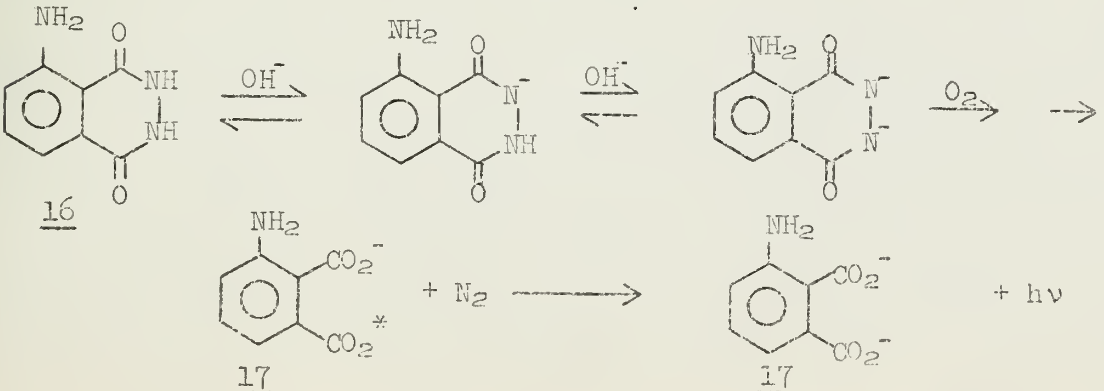


15

and the corresponding silyl anion 15. Extremely bright light is observed when this mixture is then oxidized by air or dibenzoyl peroxide. The identity of the emitter is however unknown since the chemiluminescence spectrum does not match the fluorescence spectrum of 13. Biphenyl radical anions produce no chemiluminescence under comparable conditions. Since triphenylsilanide (ϕ_3Si^-), produced by reduction of hexaphenyldisilane or triphenylchlorosilane, affords significant light emission when it reacts with oxygen,[22] it is possible that anion 14 is involved in the chemiluminescent reaction of 13. It has been suggested that oxygenation of either the organosilanide anion 15 or corresponding radical is causing light emission. At any rate, a more definitive study in this area is needed.

Of all organic compounds studied producing chemiluminescence, the most widely studied is 5-amino-2,3-dihydro-1,4-phthalazinedione (luminol) 16. It was first studied in 1928, and since then, some 200 papers have been written concerning reactions of luminol and similar derivatives. Since these studies have been extensively reviewed,[2a,b,d,e] only recent developments in these studies will be reported here. Generally, luminol has been reacted in protic and aprotic systems with the general mechanism depicted in Scheme VI. The protic system used was H$_2$O, base, hydrogen peroxide and ferricyanide,

Scheme VI



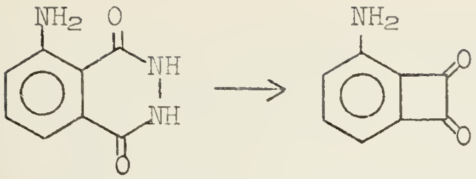
hypochlorite or some other catalyst. Simpler systems in aprotic solvents can be used. For example, in DMSO, only a strong base and oxygen are necessary. The singlet excited state of 3-amino phthalate, 17, has been shown to be the emitter and the oxygen present was shown to come from O_2 by labeling studies. Azaquinones have also been isolated as intermediates in luminol reactions.[23]

Recent studies on the mechanism of luminol chemiluminescence have appeared which concentrate on a difference in the chemiluminescence spectrum in DMSO and aqueous system.[24,25] In DMSO solutions, Gorsuch and Hercules[25] studied the equilibrium of the sodium salt of luminol with the dianion of luminol ($lum^=$). The monoanion was found not to be chemiluminescent. The chemiluminescence spectrum of luminol in DMSO and in DMSO with small amounts of H_2O are identical. Higher water concentration results in a new band at 410 nm. A difference in the fluorescence and chemiluminescence spectra in 15-40% H_2O in DMSO is found. This was thought to arise from absorption by Na^+LuM^- present. A drastic effect on the chemiluminescence intensity is found on addition of H_2O to DMSO, and the luminescence decay times in stopped flow experiments are also increased. It was concluded that in DMSO the dianion is the reacting species and that the equilibrium of monoanion and dianion requires excess base to shift it toward the dianion. In aqueous systems, formation of the dianion is not expected and hence a catalyst and hydrogen peroxide are required to initiate the reaction by removal of a hydrogen atom from the monoanion. Small amounts of water in DMSO shift the equilibrium toward the monoanion. The fluorescence band of the 3-aminophthalate dianion 17 at 490 nm in DMSO is attributed to an excited state species where a proton is transferred from the amino group to the adjacent carbonyl group,[24,25] whereas the high energy band is due to 17 without proton transfer. A blue-shift in DMSO-H_2O mixture, relative to H_2O, for the high energy band can be attributed to the greater combined dipole and hydrogen bonding effects in H_2O which stabilize the polar charge-transfered species. This study thus supports the mechanism shown in Scheme VI with the possibility of some oxygen bridge intermediate forming in the reaction of O_2 with $LUM^=$. The dianion, $LUM^=$, was also implicated in a study of luminol reaction with aqueous base, potassium ferricyanide, and O_2 (no H_2O_2).[26] Here a semidione structured intermediate was postulated to be forming by a one electron reversible oxidation of $lum^=$ by ferricyanide. The semidione then reacts with O_2, producing light, or is destroyed by ferricyanide in the absence of O_2. A study of the quantum yields of various substituted phthalazinediones was made[27] in an aqueous heminhydroxide system, where it was found that electron donating substitutents stabilize the excited state of the product (phthalate dianions) relative to ground state of the product and thus increase crossing to the excited state and the overall quantum yield.

Dicarboxylic acids were found to influence the chemiluminescence of luminol in the aqueous base, ferricyanide, O_2 system.[28] Several organic acids (ie. succinic acid) were found to increase the light yield when added. The increase was found to be roughly dependent on the number of carboxylate anions present. It was postulated that carboxylic free radicals may have been forming by reaction with ferricyanide.

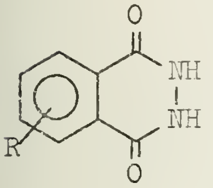
Some new methods of generating chemiluminescence using luminol have recently been reported. By using ^{32}P as a source of radiation in aqueous base, luminol produces light some 22 times more intense than in the purely chemical system.[29] It is observed that free radical concentration in this system is lower than in the usual aqueous system which should disfavor dark reactions. Luminol is also oxidized by ferrocene-lead peroxide generation of ferricinium ion.[30] This ferricinium ion is more efficient than ferricyanide as an oxidizing agent of luminol. Luminol has been recently oxidized by tert-butylhypochlorite in acetone at -10° producing, presumably, the semidione intermediate.[31] On warming to room temperature, no light is given off, but 10 fluorescent products were reported to have been isolated. The major product appears to be dione 18 formed in over 70% yield. Luminol has been

photo-oxidized in the presence of methylene blue sensitizers.[32] It was observed that the product of the reaction is 3-amino phthalate, but some light is also obtained at 520 nm which corresponds to the fluorescence of methylene blue. It was postulated that singlet oxygen is produced which reacts with base forming an unknown oxidizing species which reacts with luminol producing light.



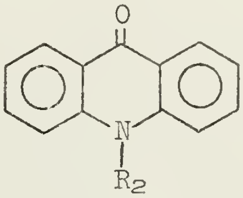
16 18

A considerable amount of work has recently been done using cyclic hydrazides like luminol to produce an excited state product, and then transferring the energy to a more efficient fluorescer. Fluorescein dye when added to luminol being oxidized in an aqueous system gives a 33% increase in intensity of the light produced along with a change in wavelength of the emitted light from 425 nm to 525 nm which corresponds to the fluorescence spectrum of fluroescein.[33] Compounds of the type A-B have been designed where B is a moiety such as luminol which can easily produce an excited

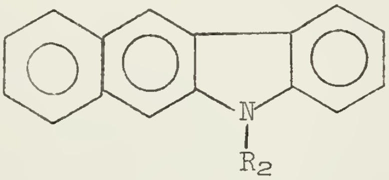


19

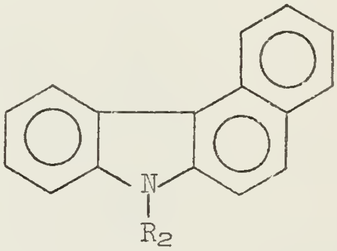
a) R=H
b) R=3-Me
c) R=4-Me



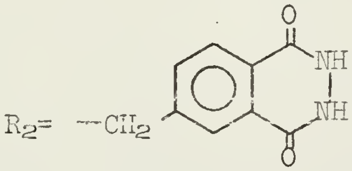
20

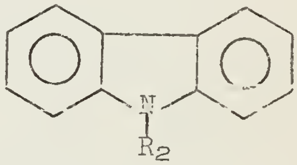


21

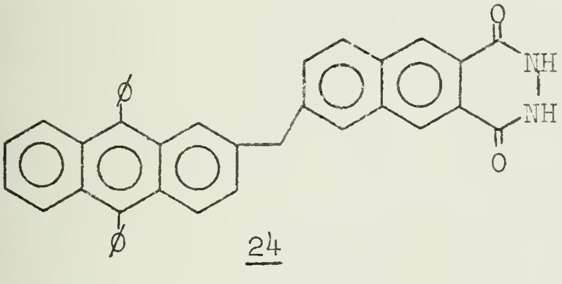


22

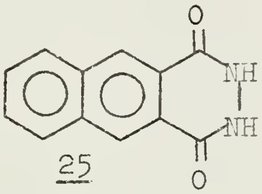




23



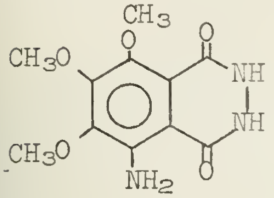
24



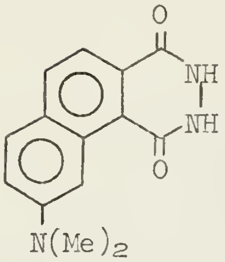
25

state product, and A is an efficiently fluorescent moiety which can accept the energy from B going to its first excited state, and then emit energy on returning to its ground state. Derivatives of luminol 19 a-c are chemiluminescent in DMSO but not in aqueous systems.[34] The emitter in these cases are anions of the cyclic hydrazides since the corresponding phthalate dianions are completely non-fluorescent in either aqueous or aprotic media, so an intermolecular energy transfer seems to be occurring here. Compounds 20 to 23 have been found to be chemiluminescent under typical luminol reaction conditions[34] with the emission matching the fluorescence of the acceptor groups shown. The decrease in intensity going from 20 to 23 is somewhat of an anomalous effect, since by comparing overlap of absorption bands, 22 should have the most intense emission. A triplet-singlet energy transfer is postulated. Other difunctional compounds of the type 24 were studied[35] in which the emission is only from the diphenylanthrancene protion of the molecule in 90% DMSO/*tert*-butanol. In an aqueous system, emissions were found from both portions of the molecule. Mixing hydrazide 25 and 9,10-diphenylanthracene gives little light in a DMSO system so energy transfer occurs intramolecularly.

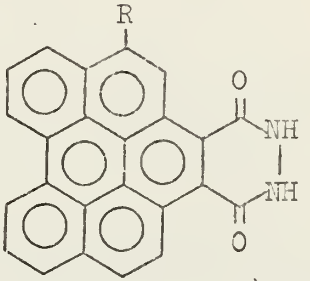
Cyclic hydrazides have recently been synthesized by White and Wei[36] which are much more efficient than luminol. The quantum yield for chemiluminescence (ϕ_{CH}) for luminol is 1.25%. Compounds 26 and 27 were found to be 30% and 150% more efficient than luminol in DMSO. Compound 28a has the highest ϕ_{CH} so far recorded for a hydrazide of 7.3% with emission as usual from the corresponding dianion. Compound 28b has ϕ_{CH}=7% and here a steric effect of the peri-hydrogen leads to instability and hence lower emission than expected.



26

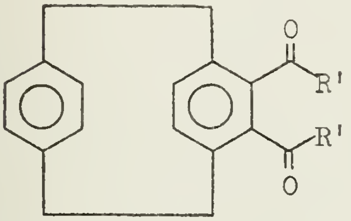


27



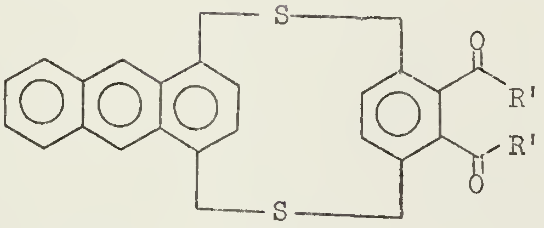
28

a) R=H
b) R=N(CH_3)$_2$

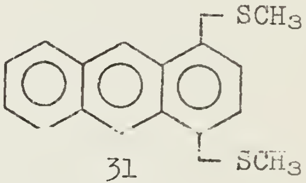


29

a) — R'-R'-=— NH-NH-
b) R'=OCH_3



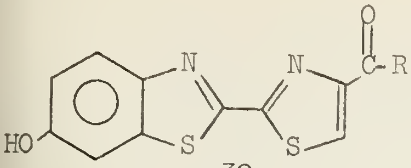
30



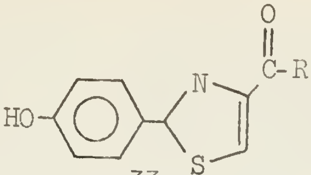
31

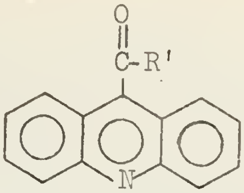
Recently an extremely interesting group of chemiluminescent compounds exhibiting energy transfer have been synthesized.[37] They make use of a cyclophane ring structure as seen in compounds 29a and 30a. These paracyclophanes have both emitter and fluorescer situated parallel to each other which seems to favor the energy transfer process. The chemiluminescence of 29a in DMSO/t-BuOK systems shows emission at 395 nm and the [2.2] paracyclophane 29b fluoresces at 355 nm. Light emission of 29a is weaker than 30a but is still much improved relative to the unsubstituted cyclic hydrazide in DMSO. Mixtures of 31 and 2,3-dihydro-1,4-phthalazinedione produce only 1/25 as much light as 30a showing energy transfer to be intramolecular.

The chemiluminescence of linear hydrazides has recently been studied by White and co-workers.[38] Compounds of the structure 32-35 were studied in DMSO, base, and O_2. It was found that unsubstituted hydrazides (ie. 32a, 33a, 34a) had highest quantum yields. In 32a and 33a the chemiluminescence spectrum matches the fluorescence spectrum of the corresponding acid anions 32c and 33c. The chemiluminescence spectra of the 9-acridine carboxylic acid hydrazides matches the fluorescence spectra of a mixture of the acids and acridone. No light was observed from 32b, 33b, 34b, 33d, or 35. An acyl anion was postulated as a reactive intermediate with electron transfer to the anti-bonding orbital of the radical cation producing the corresponding acids in the excited state.

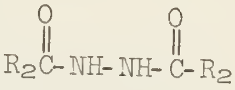

32

a) R=-NH-NH$_2$
b) R=-NH-NH-CH$_3$
c) R=OH


33

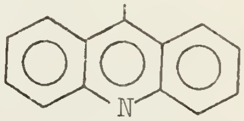

34

a) R'=-NH-NH$_2$
b) R'=-N(CH$_3$)-N=CHCH$_3$
c) R'=-NH-NH-CH$_3$
d) R'=-NCH$_3$-NH$_2$


35

$R_2\overset{O}{\overset{\|}{C}}\text{-NH-NH-}\overset{O}{\overset{\|}{C}}\text{-}R_2$

R$_2$ =



Chemiluminescent reactions of various peroxides and dioxetanes have been observed. Weak chemiluminescence from benzoyl peroxide in pyridine has been observed[39] although the emitter was not identified. Rubrene or naphthacene was added, changing the spectrum to the wavelength of fluorescence of the added fluorescer by an energy transfer processes. Phthaloyl peroxide in DMSO with potassium tert-butoxide and fluorescein emits a weak light.[40] However, with 9-10 diphenylanthracene present, phthaloyl peroxide, on heating to 50-70°, gives a relatively strong chemiluminescence. Photoperoxides of aromatic hydrocarbons decompose on heating or by acid induced cleavage to produce light.[42] The dioxetane ring structure was found to decompose thermally producing excited state products. Thermal decomposition of tetramethyl-1,2-dioxetane has been studied by Turro and Lechtken[43] in which both triplet and singlet state products were produced. The singlet state is responsible for chemiluminescence which is increased by increasing oxygen concentration. Trimethyl-1,2-dioxetane has been thermally decomposed in the presence of europium chelates as fluorescent acceptors[44] giving a rather efficient production of light (ϕ_{CH}=1.5 x 10^{-2} einsteins/mole) of very narrow bandwidth. The synthesis and chemiluminescence of 4-*t*-butyl-1,2-dioxetan-3-one, an α-=peroxylactone, has recently been described by Adam and coworkers.[45,46] This reaction in the presence of rubrene was found to increase light emission by a factor of 10^3.

In conclusion, it can be seen that a wide variety of new chemiluminescent systems have been studied in the last few years, and much work on the mechanism of light production of known systems has been described. There is, however, still much work to be done in this area for practical as well as theoretical reasons. The possibility of devising systems capable of "photochemistry without light" has been suggested by White and Roswell in 1970,[2e] where the excited state energy of a compound produced chemically can be transferred to another compound producing a chemical reaction in the second compound. Such work has been started by White where trimethyl-1,2-dioxetane was decomposed in the presence of *trans*-stilbene producing 41% isomerization of the stilbene.[47] This method of producing chemical reactions has the advantages of simplicity and the assurance that in the initial stages of reaction, all excitation energy resides in one chemical species if systems which are efficient can be devised. Other potentially practical uses of chemiluminescence are evident from the fact that one pound of perfectly efficient chemiluminescent compound would provide the equivalent in light of a 40 watt incandescent bulb operating for six days.[2c] For these as well as for theoretical reasons, research in chemiluminescent systems will continue to be of importance.

BIBLIOGRAPHY

1. a) F. McCapra, Quart. Rev. 20, 485 (1966); b) B. Radziszewski, Ber., 10, 70 (1877).
2. a) K. D. Gundermann, Angew Chem. Ind. Ed., 4, 566 (1965); b) F. McCapra, Quart. Rev., 20, 485 (1966); c) M. Ranhut, Acc. Chem. Res. 2, 80 (1969); d) J. W. Haas, J. Chem. Educ., 44, 396 (1967); e) E. H. White, and D. F. Roswell, Acc. Chem. Res., 3, 54 (1970); f) F. McCapra, Pure Appl. Chem., 611 (1970); g) F. Fry, U. of Ill. Seminar, P. 106, Fall 1969.

3. a) T. Goto, Tet, 28, 4065 (1972); b) T. A. Hopkins, H. Seliger, E. H. White, M. Cass, J. Amer. Chem. Soc., 89, 7148 (1967); c) E. H. White, E. Rapaport, T. Hopkins, H. Seligar, ibid., 91 2178 (1969).
4. N. Suzuki, T. Goto, Tet. Lett, 2021 (1971).
5. M. DeLuca and M. Dempsey, Bioch. Biophs, Res. Comm., 40, 117 (1970).
6. P. Plant, E. H. White, and U. McElroy, Bioch. Biophys. Res. Comm. 31, 98 (1968).
7. N. Suzuki, M. Sato, K. Okada, and T. Goto, Tet., 28, 4065 (1972).
8. N. Suzuki and T. Goto, Tet. 28, 4075 (1972).
9. T. Goto, Pure Appl. Chem., 17, 421 (1968).
10. Y. Kishi, T. Goto, Y. Hirata, O. Shimomura, and F. Johnson, Tet. Lett., 3427 (1966).
11. Y. Kishi and T. Goto, Tet. Let., 3427 (1966).
12. T. Karpetcky and E. H. White, J. Amer. Chem. Soc., 93, 2333 (1971).
13. Y. Kishi, T. Goto, S. Inone, S. Sugiura and H. Kishimoto, Tet. Lett., 3445 (1966).
14. F. McCapra and M. Roth, J. Chem. Soc. Ch., 894 (1972).
15. F. McCapra and Y. Chang, Chem. Comm., 1011 (1967).
16. T. Goto, M. Isobe, D. Coviello and Y. Kishi, Tet., 29, 2035 (1973).
17. Y. Kishi, H. Tanino and T. Goto, Tet. Lett., 2747 (1972).
18. O. Shimomura and F. Johnson, Tet. Lett., 2963 (1973).
19. K. Hori and H. Cormier, PNAS, U.S., 70, 120 (1973).
20. M. DeLuca, M. Dempsey, K. Hori, J. Wampler and M. Cormier, PNAS, U.S., 68, 1658 (1971).
21. E. G. Janzen, W. Harrison and G. Dubose, J. Orgmet. Chem., 40, 281 (1972).
22. E. Janzen, W. Harrison, and J. Pickett, J. Orgmet. Chem., 20, p. 13, (1969).
23. a) E. H. White, E. Nash, D. Roberts and O. Zafiriou, J. Amer. Chem. Soc., 90, 5932 (1969); b) K. D. Gundermann, Ann., 743, 200 (1971); c) K. D. Gundermann, H. Fiege and C. Klockenbring, ibid., 738, 140 (1970).
24. J. Lee and H. Seliger, Photoch. P., 11, 247 (1970).
25. J. Gorsuch and D. Hercules, Photoch. P., 15, 567 (1972).
26. P. Shevlin and H. Neufeld, J. Org. Chem., 35, 2178 (1970).
27. R. Brundrett, D. Roswell and E. White, J. Amer. Chem. Soc., 94, 7536 (1972).
28. J. Nikokavouras and G. Vasilopoulos, Z. Phys. Chem. F., 75, 180 (1971).
29. J. Nikokavouras, A. Mantaka, D. Marketos, N. Rakentzis, and G. Vassilopodos, Z. Phys. Chem. F., 78, 76 (1972).
30. T. Matsumoto and M. Sato, Chem. Lett., 869 (1972)
31. J. Nikokavouras, A. Perry and Vassilopoulos, Isr. J. Chem., 10, 19 (1972).
32. I. Matheson and J. Lee, Photoch. P., 12, 9 (1970).
33. J. Nikokavouras and G. Vassilopoulos, Z. Phys. Chem. F., 71, 138 (1970).
34. D. R. Roberts and E. H. White, J. Amer. Chem. Soc., 92, 4861 (1970).
35. D. F. Roswell, V. Paul and E. H. White, ibid., 92, 4855 (1970).
36. C. Wei and E. White, Tet. Lett., 3559, (1971).
37. R. D. Gundermann and K. Roker, Angew. Chem. Int. Ed., 12 425 (1973).
38. E. Rapaport, M. Cass and E. White, J. Amer. Chem. Soc., 94, 3153 (1972).
39. M. Whitehouse and K. Jennings, J. Chem. Soc.(B), 1453 (1970).
40. Lie, Ann, 738, 140 (1970).
41. K. Gundermann, M. Steinfalt, and H. Fiege, Angew. Chem. Int. Ed., 10, 67 (1971).
42. G. Lundeen and Adelman, J. Amer. Chem. Soc., 92, 3914 (1970).
43. N. Turro, P. Lechtkeen, J. Amer. Chem. Soc., 94, 2886 (1972).
44. P. Wildes, E. White, ibid., 93, 6286 (1971).
45. W. Adam and J. Kin, ibid., 94, 2894 (1972).
46. W. Adam and H. Steinmetzer, Angew. Chem. Int. Ed., 11 540 (1972).
47. E. White, J. Wiecko, D. Roswell, J. Amer. Chem. Soc., 91, 5194 (1969); b) E. White, P. Wildes, J. Wiecko, H. Doshan and C. Wei, J. Amer. Chem. Soc., 95, 7050 (1973).

CONTROVERSIAL STEREOCHEMICAL INTERPRETATIONS OF NUCLEOPHILIC ADDITIONS (H$^\ominus$ AND R$^\ominus$) TO KETONES

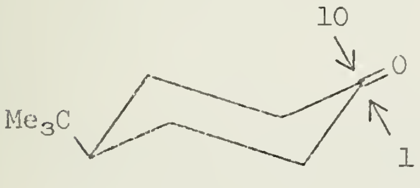
Report by May D. Lu November 26, 1973

INTRODUCTION

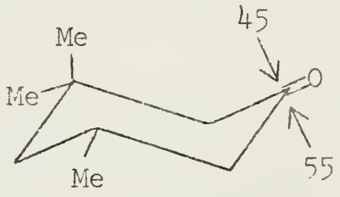
The stereochemical outcome of ketone reductions with complex metal hydride reagents is a problem which has attracted the attention of many workers. One of the earliest and most descriptive postulates concerning the stereochemical results is that of Cram and Greene[1] who considered that the reduction of acyclic ketones by lithium aluminum hydride proceeds by the formation of an initial complex between the hydride and the carbonyl oxygen atom and, in this complex, the oxygen "becomes effectively the bulkiest group in the molecule and tends to orient itself between the two least bulky groups attached to the adjacent asymmetric carbon atom." The predominant isomer "would be formed by approach of the entering group from the least hindered side of the carbonyl complex." In 1956, Dauben and coworkers proposed the classical postulate in this area[2] based on the reduction of substituted cyclohexanones of differing steric requirements with metal hydrides of differing steric bulk. They considered that the reduction process involves a preliminary formation of a metallo-organic complex between the carbonyl group and the hydride species, and it is in this complex that hydride transfer occurs. Two features of the reduction were considered, "first, the ease of formation of the initial complex or steric approach control and second, the relative energetics of the formation of the products once the complex was formed or product development control." Later the terminology was extended to reactions of cyclohexanones with nucleophiles other than hydrides.

It has never been questioned that "steric approach control," i.e. crowding of the incoming nucleophile in the transition state, is an important factor in determining the stereochemistry of some ketone reactions. However, doubts have been expressed regarding the reality of "product development control."[3-7] Over the years, explanations of the stereochemistry of these reactions based on pure steric approach considerations,[4] or on different aspects of eclipsing effects[5] have been advanced. However, as pointed out by Wigfield and Phelps, the majority of these workers in rationalizing the axial : equatorial product ratios have lent their support to explanations involving early transition states. The conclusions they drew have rarely rested on any experimental evidence other than the product ratios they are supposed to explain. More recently, workers having other views on the nature of the transition state have concluded that borohydride and aluminohydride reductions pass through a product-like transition state.[9-11] In the following discussion, different approaches adopted by the various workers in this area are presented.

STERIC APPROACH CONTROL VS. PRODUCT DEVELOPMENT CONTROL



1



2

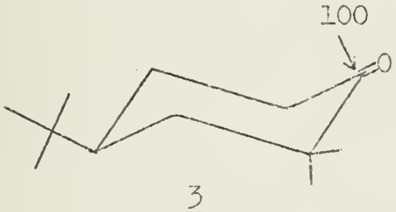
4-*tert*-Butylcyclohexanone (1) provides a text-book example of "product development control". Upon reduction with lithium aluminum hydride the more stable (equatorial) alcohol, *trans*-4-*tert*-butylcyclohexanol, predominates[12] over the less stable *cis* (axial) diastereomer by a factor of 10 to 1. In contrast, mild "steric approach control" is seen in 3,3,5-trimethylcyclohexanone (2) in which the more stable[13] equatorial alcohol is now the minor product (45%) while the axial alcohol formed by approach of the hydride from the less hindered equatorial side, predominates (55%).[14]

One major argument against "product development control[15]" is that the reduction of ketones by borohydrides or aluminohydrides are highly exothermic reactions with low activation energy. For this type of reaction, the Hammond postulate[16,17] suggests that the transition state should resemble the starting material rather than the product. Therefore there is no obvious reason why the relative stability of the epimeric products should be reflected in the transition states leading to them. Another opposing argument is based on the finding[12] that the more stable equatorial alcohol is formed in the lithium aluminum hydride reduction of 1 in greater proportion (10:1) than the corresponding equilibrium ratio (2.4:1)[18] of the alcohol.

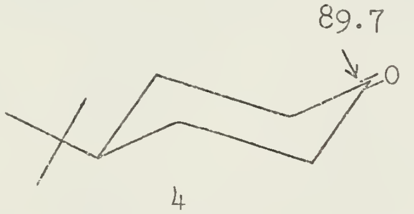
THE ALL-STERIC PROPOSAL

In the belief that "product development control" might not prove a satisfactory explanation of the observed product ratio in the reduction of 1, alternative explanations have been devised.

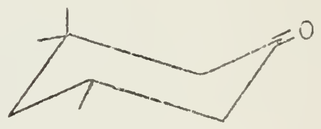
In 1965, J. C. Richer proposed an explanation of the observed stereochemistry based solely on steric factors.[4] The addition of a number of small (hydride and cyanide ions) or linear like substituents ($-CH_2NO_2$, and $-C\equiv C-H$) to 4-*tert*-butylcyclohexanone (1) was considered and it was found that the equatorial alcohols were produced in 90:10 excess in all cases, thus, axial attack is favored over equatorial attack. It was considered that the hydrogens in positions 2 and 6 are not disposed symmetrically above and below the plane of the carbonyl group. Instead the equatorial hydrogens are in the plane of the carbonyl group and do not interfere with the approach of nucleophiles from either side of the carbonyl group. The axial hydrogens are perpendicular to the plane of the carbonyl group and will interfere with the approach of nucleophiles from the equatorial side but not from the axial side. It was suggested that the stereochemical courses of all the additions on unhindered ketones by groups small enough not to interfere with the axial hydrogen in positions 3 and 5 would be directed exclusively by the presence of the axial hydrogens in position 2 and 6 which hinder attack from the equatorial side. This all-steric proposal was further supported by the observation that 4-*tert*-butyl-2,2-dimethylcyclohexanone (3) reduction with $LiAlH(O^{-}t\text{-}Bu)_3$ gave more axial attack than its unmethylated analog (4). On the other hand, the observation is contrary to what would be predicted by "product development control" since 4-*tert*-butyl-2,2-dimethylcyclohexanols give more axial -OH at equilibrium than do the 4-*tert*-butylcyclohexanols. According to the all steric proposal, as the size of the entering group becomes larger, more and



3



4

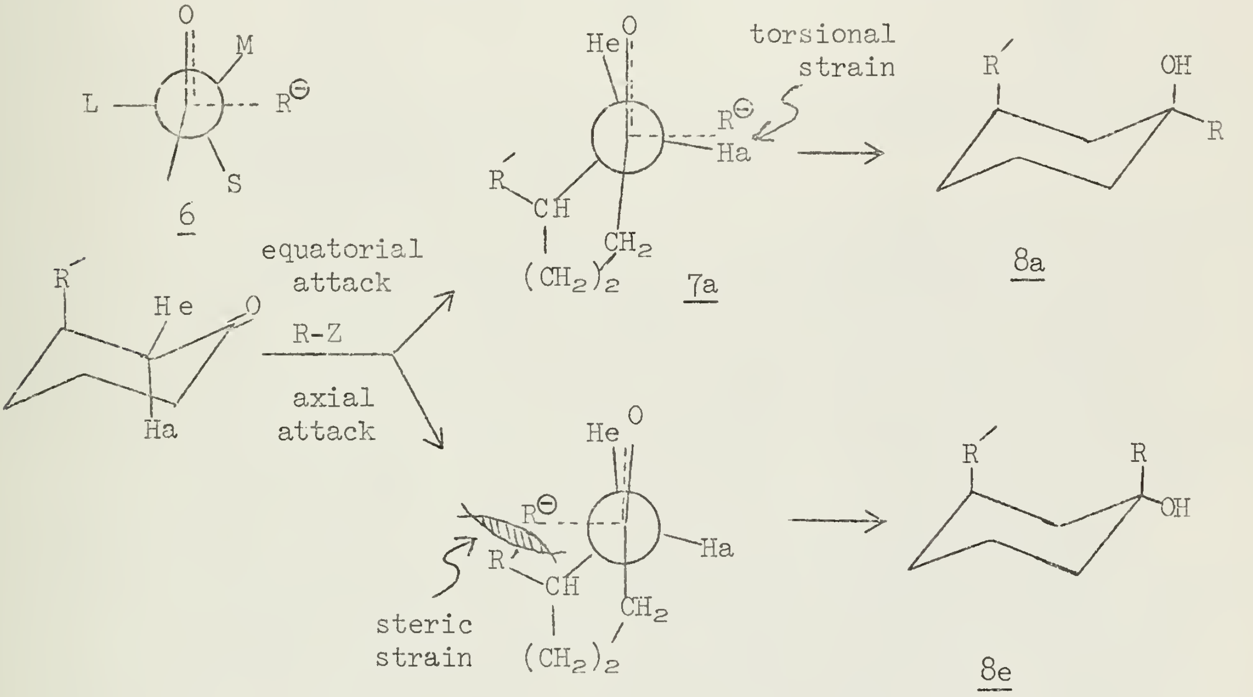


5

more interactions with the 3 and 5 axial hydrogens will be felt, favoring to a greater extent the equatorial attack on the ketone. This point is supported by the axial introduction of a methyl group (methylmagnesium iodide) to 4-*tert*-butylcyclohexanone in which more than 50% equatorial attack was observed.[19,20] It was noted that the axial introduction of a hydride ion (from LiAlH$_4$) on 3,3,5-trimethylcyclohexanone (5) would provoke in the transition state of axial attack, a 1_a-H-3_a-CH$_3$ interaction leading to a mixture of isomeric alcohols containing approximately equal parts of each.[21] At the time, it was felt that it was possible to explain all the stereochemical results of the hydride reduction of cyclic ketones on the basis of steric factors alone.

STERIC INTERACTION VS. TORSIONAL STRAIN

Felkin and his coworkers adopted a different approach to the interpretation of the observed steric outcome. In 1968, they proposed an explanation which they claimed to be applicable to both open-chain carbonyl compounds and cyclohexanones.[5] The proposed explanation involved torsional strain and steric interactions and ascribed the observed axial : equatorial ratio to the relative magnitude of these interactions. According to Felkin, "there is no need to assume a change in the preferred transition state from one that is essentially reactant-like in the case of sterically hindered cyclohexanones, to one that is essentially product-like in the case of unhindered cyclohexanones." They felt both torsional strain and steric strain can be minimized simultaneously in a reactant-like transition state (6) when the substrate is acyclic. This is not possible in the case of cyclohexanones. Since the formation of the axial alcohol 8a implies a partially eclipsed transition state, 7a, involving some degree of torsional strain, and the formation of the equatorial alcohol 8e implies an essentially staggered transition state, 7e, involving some degree of steric strain.



6

7a

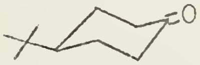
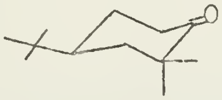
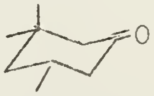
8a

8e

7e

They proposed that these reactions all proceed via reactant-like transition states and the steric outcome is determined by the relative magnitudes of torsional strain in 7a and steric strain in 7e. With small $R^{\ominus}$ and R', the transition state 7e is preferred since the steric strain in this case is expected to be smaller than the torsional strain. Transition state 7a becomes the preferred one as the size of $R^{\ominus}$ and/or R' increases, since under this condition the steric strain in 7e is increased while the torsional strain in 7a is expected to remain essentially unchanged. As seen in the reduction of 4-*tert*-butylcyclohexanone (R' = H), 4-*tert*-butyl-2,2-dimethylcyclohexanone (R' = H), and 3,3,5-trimethylcyclohexanone (R' = Me) by lithium aluminum hydride ($R^{\ominus} = H^{\ominus}$), over 90% of the equatorial alcohol (via 7e) is formed in the first two cases while less than 50% of the more stable equatorial alcohol is formed from 3,3,5-trimethylcyclohexanone (Table I). A more clear cut example is seen in the reduction of the same

Table I.

reagent	% of equatorial alcohol formed (axial attack)		
			
LiAlH$_4$	90-91[7]	94[7]	37-42[7]
NaBH$_4$	87[22]	92[4]	38[22]
LiAlH(Ot-Bu)	90[4]	100[4]	12[4]
(CH$_3$)$_3$Al	15[23],#		0[23],*

# in diethyl ether solvent.
* 1:1 ratio of AlMe$_3$/ketone, in benzene solvent.

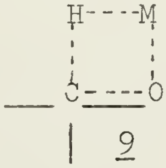
series of cyclohexanones with LiAlH(O-t-Bu)$_3$. An increase in the "effective bulk" of the reagent should also make 7a the preferred transition state, this is reflected in the stereochemistry of the alkylation of 4-*tert*-butylcyclohexanone as compared to its reduction. In both alkylations, a much higher proportion of the axial alcohol is formed than in the reductions. However, as pointed out by Felkin, the "effective bulk" of the reagent is not always easy to assess, since it is dependent not only on the "intrinsic bulk" of R, but also upon solvation, the length of the $R^{\ominus}$---C bond in the transition state, and the mechanism whereby $R^{\ominus}$ is being transferred from metal to carbon. From a study of the ratios of the isomeric products obtained in the reaction between 4-*tert*-butylcyclohexanone and *tert*-butylallyl magnesium bromide, the authors further concluded that the factor which impedes the formation of the axial alcohol can not be steric strain involving $R^{\ominus}$ and H_a in the transition state 7a[24] According to them the stereochemistry of the reaction of simple cyclohexanones with hydrides and Grignard reagents is determined by the net difference between the steric strain in transition state 7e, leading to the equatorial alcohol and the torsional strain in transition state 7a, leading to the axial alcohol.

EVIDENCE FOR A LATE TRANSITION STATE

In a study on the relative rates of reduction of a series of substituted cyclohexanones with differing steric requirements[7], Eliel and Senda have also concluded that "product-development control", i.e. the reflection

of the greater stability of the equatorial as compared to the axial products in the corresponding transition states, can at best explain a minor part of the preference for the equatorial products. From the ratio of the rate constant (never in excess of 14) for the formation of the axial alcohol from the reduction of 4-*tert*-butylcyclohexanone (4) and 4-*tert*-butyl-2,2-dimethylcyclohexanone (3)[7], they also concluded that it is unlikely that the steric encumbrance of the axial hydrogens at C-2 and C-6 play a major role in controlling the steric course of the reaction as the all steric proposal of J. C. Richer implies.

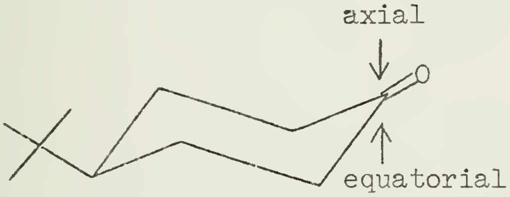
Lamaty and coworkers[9], on the basis of Hammett relationships[25,26] have concluded that the borohydride reduction of ketones passes through a product-like transition state. Other workers[11] have also argued, on the basis of the breakdown of a model for carbonyl additions, that the transition state for borohydride and aluminohydride reduction of aldehydes is also product-like. The most commonly accepted transition state for hydride reduction is of the type shown in structure 9.[27] It implies that the



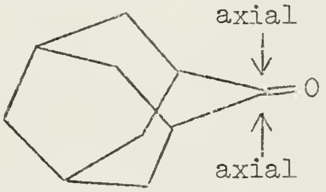
9

hybridization of the C-O bond has changed substantially from sp^2 to sp^3 and that C-H bond formation has also proceeded appreciably in the transition state, contrary to what had been inferred from the Hammond postulate.[15] It does not, however, as pointed out by Eliel and Senda[7], imply that the geometry of the transition state is tetrahedral, since the strain involved in the four-membered ring will prevent it from becoming so. This, they suggested, was the reason for the absence of "product development control" as observed experimentally.

Lamaty and his coworkers have also published evidence which "prove beyond any reasonable doubt that the transition state is product-like" in the borohydride reduction of ketones.[10] Their evidence came from the comparison of rates of attack on 4-*tert*-butylcyclohexanone (10) and adamantanone (11) by the

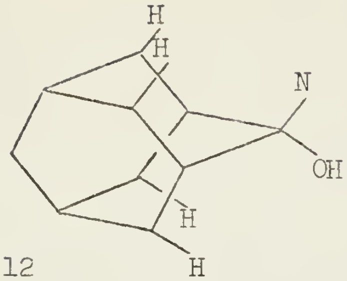


10



11

borohydride and the sulfite anions. As can be seen easily from a model, both sides of the adamantanone molecule are the same and are like the axial side of 4-*tert*-butylcyclohexanone. Two situations were considered. First, when the transition state is "reactant-like", the incoming nucleophile is still quite far from the electrophilic carbon which is still in a sp^2 hybridization state. When the nucleophile approaches the adamantanone molecule from either direction, it "sees" the axial side of 4-*tert*-butylcyclohexanone. Therefore the rate of addition to adamantanone, k_α, would be approximately equal to 2 k_a, k_a being the rate of axial attack on 4-*tert*-butylcyclohexanone. However if the transition state is "product-like", the central carbon would be in a sp^3 state and both the -OH group and the nucleophile N would be axial to one side or the other of the adamantanone molecule (12). When N is small, such as a hydride ion, the situation is the same as that resulting from equatorial



12

attack on the 4-tert-butylcyclohexanone molecule, and the rate constant k_α will be expected to be approximately equal to 2 k_e, where k_e is the rate constant of equatorial attack on 4-tert-butylcyclohexanone. It was found that $k_\alpha \approx 2k_e$ for borohydride attack. Therefore they "proved beyond any reasonable doubt that the transition state is product-like" in the borohydride reduction of ketones. However Wigfield[8] and Phelps pointed out that since the attack from either side of the carbonyl group in adamantanone is equivalent (being equatorial to one ring and axial to the other), attacking at this center from either side is equivalent to attack at the least favored side of 4-tert-butylcyclohexanone, regardless of whether this happen to be axial or equatorial. Since there are two equivalent sides to attack, one would then immediately predict that $k_\alpha \approx 2k_u$, where k_u is the rate constant for attack at the least favored side of 4-tert-butylcyclohexanone by the appropriate nucleophile. This is the result observed in both cases, and thus it would seem that the evidence given does not constitute an unambiguous proof for a late transition state in the borohydride reduction of ketones.

More recently, Wigfield and Phelps measured the kinetics of reduction of various ketones by sodium borohydride and sodium borodeuteride and determined the deuterium kinetic isotope effects.[8,28] They found that the k_H/k_D values are almost constant and show no systematic variation despite considerable product ratio changes. There is no trend towards lower isotope effect with formation of a greater proportion of axial isomer (equatorial attack) as would be anticipated if the steric approach-product development control were operative. They also found that the isotope effects are all inverse. Since the observed isotope effect is the composite of the primary isotope effect of the hydride being transferred superimposed on the secondary isotope effects of the three hydrides not being transferred, the primary isotope effect itself must be very small to be overshadowed by the secondary isotope effects. This small primary isotope effect was considered to be consistent with an early transition state as required by other explanations of the product ratios.[4,4,29] On the other hand it is also consistent with a very late transition state, where the hydride has been substantially transferred.

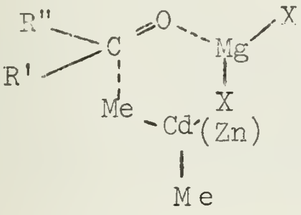
STEREOCHEMISTRY OF ALKYLATION BY ORGANOMETALLIC REAGENTS

Although organometallic alkylation reactions have found extensive applications in synthesis, the stereochemistry of these reactions has attracted much less attention than the metal hydride reduction of ketones. One of the first comprehensive studies concerning the stereochemistry of alkylation of cyclic ketones by organometallic compounds was reported by Houlihan[20]. Methyl Grignard reagents were allowed to react with 4-tert-butylcyclohexanone in diethyl ether and with all reagents studied, the axial 4-tert-butyl-1-methylcyclohexanol was always found in 50% or greater yield. Thus, attack by the methyl group was found to occur predominantly from the least hindered side of the carbonyl group, i.e. the equatorial side. It was also reported that with the

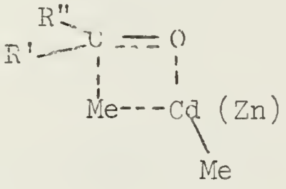
methylmagnesium salt of 3-methyl-3-pentanol in a halide free system, the 4-*tert*-butyl-1-methylcyclohexanol produced was 73-75% *trans* (axial alcohol)[30]. Thus, it is clear that magnesium reagents attack 4-*tert*-butylcyclohexanone from the less hindered equatorial side with preferential formation of the axial alcohol. On the other hand, as seen before, the addition of hydride occurs predominantly via axial attack to give the equatorial alcohol.

Marshall and Carroll[17] proposed a model for the transition state from which one could estimate semiquantitatively the magnitude of the steric effect based on the transition state bond lengths. From this model, it has been rationalized that 1,3 (diaxial) interactions are less important than 1,2 (equatorial,axial) interactions in the formation of a C-H bond, while, with the longer C-C bond being formed during Grignard addition, the importance of the interactions is reversed. Within a certain limit of bond distances, the amount of axial attack will increase as the transition-state bond distance decreases.

In a study of methylation of 4-*tert*-butylcyclohexanone by some organomagnesium, organocadmium, and organozinc reagents[31], Jones and his coworkers found that monomeric CH_3MgX (0.1 M) gives more *trans* alcohol (equatorial attack) than the corresponding associated species (0.8 M). By contrast, there was no change in reactivity or stereochemistry when the concentration of $(CH_3)_2Cd(I, Cl)$ was increased from 0.4 M to 0.9 M, or when the concentration of $(CH_3)_2Zn(I, Cl)$ was decreased from 0.3M to 0.1M. They also observed that the preference for axial attack follows the series: $(CH_3)_2Zn > (CH_3)_2Cd > CH_3MgX$. Two possible transition states of the alkylation by $(CH_3)_2M$ were considered, the six-centered transition state involving a MgX_2[32] molecule (13) and the four-centered transition state (14)[33]. Since a decrease in the reactivity of reagents because of a variation of halide present was not accompanied by any change in stereochemistry, it was considered that the transition state was reactant-like rather than product-like. As observed, the steric interference to axial attack is much smaller in Cd and in Zn reactions when compared to Mg reactions. Since methyl groups were used throughout the investigation, the lowering of steric interaction was ascribed to a tighter transition state for Cd and Zn.[17] On the basis of relative metal and halogen covalent bond distance, the six-centered transition state (13) for Mg should be tighter, leading to more axial attack, which is exactly the opposite of what is observed. On the other hand, the metal-oxygen bond is shorter for Zn and Cd compared to Mg, implying a tighter four-centered transition state which would lead to more axial attack for Zn and Cd as observed. Based on a smimilar argument, they also suggested that the observed difference in stereochemistry with 0.8 M and 0.1 M Grignard reagents is due to a tighter transition state for the associated reagents.



13



14

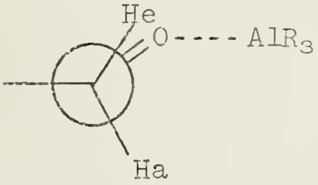
THE "COMPRESSION EFFECT"

Pasto classified steric effects that influenced stereochemistry of the product and rate of reaction into two categories: (1) remote steric effects and, (2) torsional angle effect.[34] According to his classification, both the

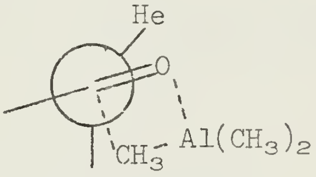
"steric approach control", and the "product development control" belong to the category of remote steric effects. The former is observed very early along the reaction coordinate while the latter is observed very late. The torsional angle effects arise from a change of hybridization at the reaction center from sp^2 to sp^3 or vice versa. During this change, an eclipsing strain energy is generated between the forming sp^3 bond and the bonds attached to the carbon alpha to the reaction center. Recently, another new concept of stereochemical control, the "compression effect", which is very similar to Pasto's torsional angle effect, was introduced by Ashby and his coworkers.[23] It was found that in the reaction of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ in benzene solvent with 4-tert-butylcyclohexanone, the predominant isomer formed is the axial alcohol when the organoaluminum compound to ketone ratio is 1:1 or less.[23,35,36] The same was true for these compounds in diethyl ether at all reactant ratios.[23] These reactions are believed to involve four-centered transition states[33,37,38] and a reasonable explanation of the stereochemistry of the products is that the organometallic reagent attacks at the least hindered (equatorial) side of the chair conformation of the ketone. When the ratio of $(CH_3)_3Al$ or $(C_2H_5)_3Al$ to ketone is 2:1 or greater in benzene solvent however, the predominant product is the equatorial alcohol arising from attack at the more hindered side of the chair conformation.[23] It was found also that, under these conditions, the transition state describing the rate-determining step contains two molecules of trialkylaluminum and one molecule of the ketone.[39] A six-centered transition state was suggested.[39]

In order to explain the unusual stereochemistry observed , it was considered that the reversal of stereochemistry in the trialkylaluminum case may be inherent in the change from a four- to a six-centered transition state.[23] Alternatively, it was considered possible that the 4-tert-butylcyclohexanone-AlR_3 complex formed in the first step of the alkylation might exist in a conformation other than a chair, thus rendering the axial side the least hindered side in a six-centered transition state. However, both of the considerations above were proved to be inadequate and a new factor, the "compression effect" was introduced to explain the observed stereochemistry.

Structure 15 illustrates the angle between the carbonyl oxygen and the



15



16

hydrogens on adjacent carbons for the 4-tert-butylcyclohexanone-AlR_3 complex. It can be seen that equatorial attack by a second R_3Al compresses the complexed carbonyl against the equatorial hydrogens in the transition state. On the other hand, axial attack leads to a staggered arrangement between the complexed carbonyl and hydrogens on adjacent carbon atoms. Thus, in the case of cyclohexanones, this "compression effect" favors attack from the more hindered side of the molecule in the 2:1-R_3Al:ketone ratio. Thus, in the above postulate, the "compression effect" and the "steric approach factor" work against each other. The reason why this "compression effect" is not observed in the case of a four-centered transition state is that, as shown in structure 16, the $(CH_3)_3Al$ molecule lies perpendicular to the plane of the carbonyl group. Since the $(CH_3)_3Al$ is on the opposite side of the carbonyl group from the groups on C-2 and C-6, which the carbonyl must eclipse in the transition state, no compression involving the $Al(CH_3)_2$ unit will occur in an early transition state. Steric approach control should determine the isomer ratio and this is what is observed.

CONCLUSION

The exact nature of the forces or interactions that govern the stereochemical course of nucleophilic additions to ketones is still unknown. None of the above postulates seems to be applicable to all the experimentally observed isomeric ratios. It is possible that all the factors brought out in the literature play some role in determining the stereochemistry of these reactions while the relative importance of these factors might vary from one reaction to the other depending on the exact nature of the transition state involved.

BIBLIOGRAPHY

1. D. J. Cram and F. D. Greene, J. Amer. Chem. Soc., 75, 6005 (1953).
2. W. G. Dauben, G. J. Fonken and D. S. Noyce, J. Amer. Chem. Soc., 77, 2579 (1955).
3. A. V. Kamernitski, A. A. Akhrem, Tetrahedron, 18, 705 (1962).
4. J. C. Richer, J. Org. Chem., 30, 324 (1965).
5. M. Cherest and H. Felkin, Tetrahedron Lett., 2205 (1968).
6. H. C. Brown, H. R. Deck, J. Amer. Chem. Soc., 87, 5620 (1965).
7. E. L. Eliel, Y. Senda, Tetrahedron, 26, 2411 (1970).
8. D. C. Wigfield and D. J. Phelps, Can. J. Chem., 50, 388 (1972).
9. P. Geneste, G. Lamaty, and J. P. Roque, Tetrahedron Lett., 5007 (1970).
10. P. Geneste, G. Lamaty, C. Moriau, and J. P. Roque, Tetrahedron Lett., 5011 (1970).
11. G. J. Karabatsos and T. G. Althuis, Tetrahedron Lett., 4911 (1967).
12. E. L. Eliel and R. S. Ro, J. Amer. Chem. Soc., 79, 5992 (1957).
13. E. L. Eliel and H. Haubenstock, J. Org. Chem., 26, 3504 (1961).
14. H. Haubenstock and E. L. Eliel, J. Amer. Chem. Soc., 84, 2363 (1962).
15. P. M. S. Wheeler and M. M. Wheeler, J. Org. Chem., 27, 3796 (1962).
16. G. S. Hammond, J. Amer. Chem. Soc., 77, 334 (1955).
17. J. A. Marshall and R. D. Caroll, J. Org. Chem., 30, 2748 (1965).
18. E. L. Eliel and S. H. Schroeter, J. Amer. Chem. Soc., 87, 5031 (1965).
19. C. H. Depuy and R. W. King, J. Amer. Chem. Soc., 83, 2743 (1961).
20. W. J. Houlihan, J. Org. Chem., 27, 3860 (1962).
21. E. L. Eliel and H. Haubenstock, J. Amer. Chem. Soc., 84, 2363 (1962).
22. P. T. Lansbury and R. E. MacLeay, J. Org. Chem., 28, 1940 (1963).
23. J. Laemmle, E. C. Ashby, and P. B. Roling, J. Org. Chem., 38, 2526 (1973).
24. M. Cherest and H. Felkin, Tetrahedron Lett., 383 (1971).
25. K. Bowden and Hardy, Tetrahedron, 22, 1169 (1966).
26. P. T. Lansbury and R. E. MacLeay, J. Amer. Chem. Soc., 87, 831 (1965).
27. P. Geneste and G. Lamaty, Tetrahedron Lett., 4633 (1965).
28. D. G. Wigfield and D. J. Phelps, Chem. Comm., 1152 (1970).
29. M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 2199 (1968).
30. H. O. House and W. L. Respess, J. Org. Chem., 30, 301 (1965).
31. P. R. Jones, E. J. Goller, and W. J. Kauffman, J. Org. Chem., 34, 3566 (1969).
32. E. C. Ashby, Qurt. Rev., 21, 259 (1967).
33. H. O. House and J. E. Oliver, J. Org. Chem., 33, 929 (1968).
34. D. J. Pasto and J. A. Gontarz, J. Amer. Chem. Soc., 93, 6909 (1971).
35. E. C. Ashby and S. Yu, Chem. Comm., 351 (1971).
36. E. C. Ashby, S. H. Yu, and P. V. Roling, J. Org. Chem., 37, 1918 (1972).
37. E. C. Ashby, J. Laemmle, and H. M. Neumann, J. Amer. Chem. Soc., 90, 5183 (1968).
38. E. C. Ashby and J. Laemmle, J. Org. Chem., 33, 3389 (1968).
39. E. C. Ashby, J. Laemmle, and H. M. Neumann, J. Amer. Chem. Soc., 90, 5179 (1968).

RECENT USES OF THE IRON CARBONYLS IN ORGANIC CHEMISTRY

Report by Arthur Haber November 29, 1973

INTRODUCTION

Carbon monoxide is a useful reagent in organic synthesis. Reductions of organic substrates with carbon monoxide at high temperatures and pressures in the presence of a transition metal catalyst;[1] carbonylation of trialkyl boranes to form alcohols, aldehydes, and ketones;[2] and the formation of aldehydes from olefins, hydrogen, and carbon monoxide in the presence of a transition metal catalyst[3] are examples of useful reactions involving carbon monoxide. The transition metal carbonyls and related compounds, both which might be considered as modified forms of carbon monoxide, have been intensively studied in recent years from the inorganic[4] and organic[5] points of view.

Of particular interest is the recent work with the iron carbonyls which has shown these reagents to be useful in carrying out deoxygenations and reductions of organic compounds, and in the formation of new carbon-carbon bonds. It is these topics which form the foundation of this seminar.

FUNCTIONAL GROUP MODIFICATIONS

Alper and coworkers' interest in iron pentacarbonyl was prompted by their observation that the parent aldehyde or ketone could be regenerated in good yield from the oxime in a refluxing solution of $Fe(CO)_5$, *n*-butyl ether, and a catalytic quantity of boron trifluoride etherate.[6]

Reactions of other compounds containing a nitrogen-oxygen bond with iron pentacarbonyl were studied.[7] It was found that amine oxides, azoxybenzenes, and nitrones were deoxygenated in good yield, while under the same conditions substituted nitro- and nitrosobenzenes were converted to azo and/or amine compounds depending on the nature and location of the substituents. Deoxygenations of a variety of *N*-nitrosoamines to give amines and in some cases ureas proceeded in good yields. A summary of the synthetic utility of these reactions is presented in Tables I-III. That brucine *N*-oxide hydrate was deoxygenated by iron pentacarbonyl in boiling butyl ether showed the general applicability of the method. Mechanisms for the deoxygenations were proposed, the first step consisting of nucleophilic attact by the oxygen atom of the substrate on the carbonyl carbon of $Fe(CO)_5$ followed by loss of carbon dioxide. For the case of aromatic nitroso compounds, a nitrene type intermediate was proposed, while for the case of *N*-nitrosoamines a tetrazene intermediate was considered. Support for these intermediates was presented.

Subsequent work by Tanaka and Anselme on the reaction of *N*,*N*-dibenzylnitrosoamine with iron pentacarbonyl gave rise to another mechanistic possibility. After the two compounds were refluxed in dioxane for 20 hours, bibenzyl, dibenzylamine, and *N*-benzylbenzaldimine were isolated in a combined yield of 67%; a 79% yield of carbon dioxide also resulted. Other experimental data was interpreted to show that there was no tetrazene intermediate and that the stoichiometry of the reaction was 1:2 in nitrosoamine and iron pentacarbonyl. However, the fact that experimental conditions were not the same in the works of Anselme and Alper must be considered.

Alper and Edward were able to effect the conversion of primary amides and thionamides to nitriles with iron pentacarbonyl in boiling butyl ether.[9] A mechanism was proposed which involved the formation of the intermediate shown in Figure 1 in the case of reaction with thionamides. Intermediates

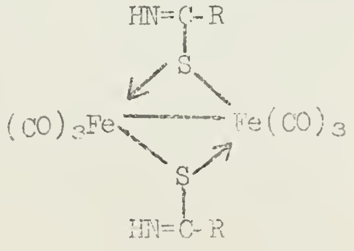


Figure 1

Amine Oxide	Yield of Amine
Pyridine	79%
2-Picoline	62
4-Picoline	78
4-Methoxypyridine	52
Quinoline	60
N,*N*-Dimethyldodecylamine	46
N,*N*-Dimethylaniline	66
Brucine	51

Table II

Reaction of *N*-Nitrosoamines with Iron Pentacarbonyl

Nitrosamine	Amine	Yield
N-Nitrosodiphenylamine	Diphenylamine	91%
N-Nitroso-*N*-phenylbenzylamine	*N*-Phenylbenzylamine	85
N-Nitroso-*N*-methylaniline	*N*-Methylaniline	90
N-Nitrosocarbazole	Carbazole	92
N-Nitrosopiperidine	Carbonyldipiperidine	48
N-Nitrosomorpholine	Carbonyldimorpholine	57

Table IV

Sulfoxide	Yield RSR
$(n\text{-}C_3H_7)_2SO$	62%
$(n\text{-}C_4H_9)_2SO$	96
$(n\text{-}C_6H_{13})_2SO$	70
$(C_6H_5CH_2)_2SO$	48
$(C_6H_5)_2SO$	91
$(p\text{-}CH_3C_6H_4)_2SO$	89
β-$CH_3SOCH_2CH_2SOCH_3$	74
$CH_3SO(CH_2)_3SOCH_3$	84
Tetramethylene sulfoxide	57
Phenoxymethyl penicillin sulfoxide methyl ester	12

Substituent	Product	Yield
H	Azobenzene	76%
o-CH_3	2,2'-Dimethylazobenzene	67
	o-Toluidine	13
m-CH_3	3,3'-Dimethylazobenzene	48
	m-Toluidine	6
p-CH_3	4,4'-Dimethylazobenzene	67
o-C_2H_5	2,2'-Diethylazobenzene	39
	o-Ethylaniline	35
o-OCH_3	*o*-Methoxyaniline	74
m-OCH_3	3,3'-Dimethoxyazobenzene	37
p-OCH_3	4,4'-Dimethoxyazobenzene	43
p-F	4,4'-Difluoroazobenzene	67
p-CN	4,4'-Dicyanoazobenzene	20
	p-Aminobenzonitrile	11
o-NO_2*	2,2'-Diaminoazobenzene	11
m-$N(CH_3)_2$	3-Amino-*N*,*N*-dimethylaniline	60
p-$N(CH_3)_2$	4-Amino-*N*,*N*-dimentylaniline	77
o-C_6H_5	2-Aminobiphenyl	58
	Carbazole	15

*Mole ratio of iron pentacarbonyl to substrate was 3.0:1 for this example; in all other cases the ratio was 1.4:1.

Table V

Sulfonyl Chloride	Yield of Ester
$C_6H_5SO_2Cl$	71%
p-$CH_3C_6H_4SO_2Cl$	48
p-$CH_3OC_6H_4SO_2Cl$	41
p-$BrC_6H_4SO_2Cl$	50
m-$NO_2C_6H_4SO_2Cl$	66
2-$C_{10}H_7SO_2Cl$	45
CH_3SO_2Cl	36
$C_{16}H_{33}SO_2Cl$	42

such as this become important in some of the other reactions of the iron carbonyls with organic substrates. It is of interest that thionamides consistently give nitriles in about twice as great a yield as the oxygen analogues.

The recent literature describes many attempts at converting sulfoxides to sulfides.[10] Included among these methods is the use of iron pentacarbonyl in either diglyme or n-butyl ether at 130-135° under nitrogen.[11] The reaction is facile and applicable to a wide variety of sulfoxides as indicated in Table IV. Two preliminary mechanistic schemes were described and some experimental support was given.

Related to these deoxygenations is the conversion of sulfonyl chlorides to thiolsulfonate esters using a 1:1 mixture of iron pentacarbonyl and boron trifluoride etherate in N,N-dimethylacetamide or tetramethyl urea.[12] Table V desicibes the applicability of this reaction. A mechanism and some experimental support were presented.

While the reaction of aromatic nitro compounds with iron pentacarbonyl has already been considered,[7] it is appropriate to consider the chemistry involved when non-aromatic nitro compounds[13] are treated with iron pentacarbonyl and when aromatic nitro compounds are treated with tri-iron dodecacarbonyl,[14] since greater insight on the actual interaction between the organic substrate and the iron carbonyl is obtained.

When the nitro compounds listed in Table VI were allowed to react with iron pentacarbonyl in dry diglyme at 120-130° for 15-17 hours, formamides and ureas resulted in low yield according to equation (1). Alper pointed out that the urea is the predominant product when the nitro compound possesses a relatively bulky alkyl group.

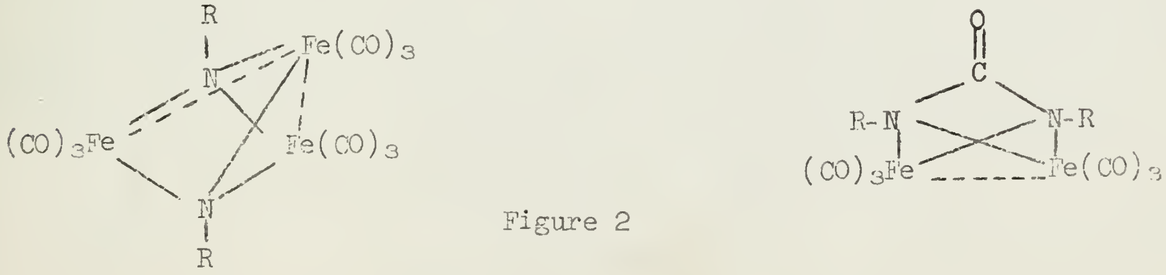
$$RNO_2 + Fe(CO)_5 \longrightarrow \underset{1}{RNHCOH} + \underset{2}{RHN\overset{O}{\overset{\|}{C}}NHR} \qquad (1)$$

Table VI

Nitro Compound	Yield 1	Yield 2
1-nitropropane	13.8%	7.4%
2-nitropropane	5.8	14.8
nitrocyclohexane	13.0	18.5
2-methyl-2-nitropropane	3.9	13.3
1-nitroadamantane	trace	9.2

The strategy that was used in attacking the mechanism of the reaction was as follows. Di-iron nonacarbonyl, a more reactive reagent than the pentacarbonyl, can effect the same reaction under milder conditions. Alper thought that by using milder conditions intermediates would be isolated (which would be the same intermediates as in the iron pentacarbonyl mediated reaction) whose structures could be determined. Subjection of these intermediates to the same reaction conditions used on the starting nitro compound might indicate the reaction pathway of equation (1).

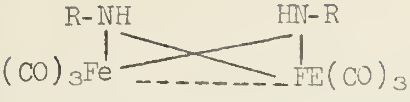
Treatment of various nitro compounds with $Fe_2(CO)_9$ at room temperature in dry benzene gave the complexes described in Figure 2, stereochemistry unspecified. Complexes of these types had been previously isolated and characterized.[15] Interconversion of complexes III-VI was shown to occur as well as their conversion to the product formamides and ureas. Analysis of these observations led to the mechanism shown in Scheme I.



III

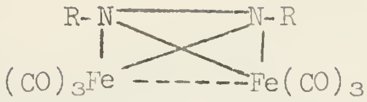
IV

Figure 2



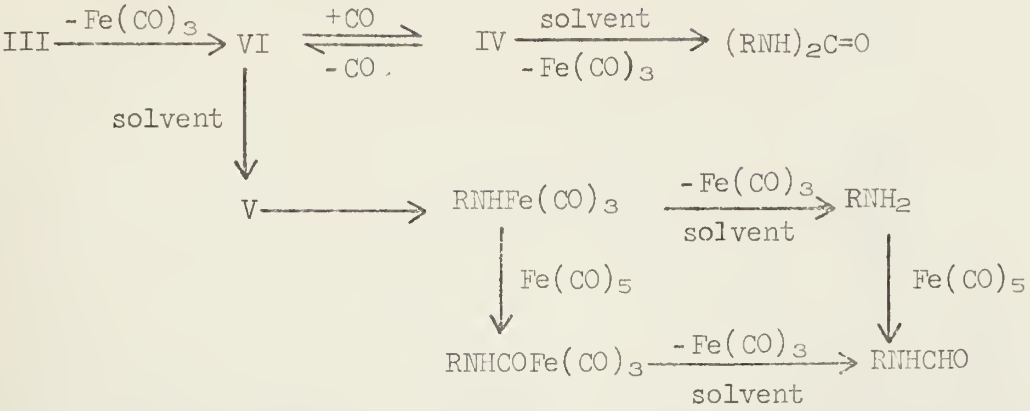
V

Figure 2 (cont'd)



VI

Scheme I



While the reaction of nitro compounds with iron pentacarbonyl gives rise to reduction and coupling products,[7] and carbonyl insertion products,[13] the reaction of aromatic nitro compounds with tri-iron dodecacarbonyl in refluxing benzene containing a small amount of methanol affords amines in high yields as shown in Table VII.[14]

Table VII

$NO_2C_6H_4X$ X	% Yield $NH_2C_6H_4X$
H	77
p-Cl	86
o-Cl	83
p-CH_3	73
o-CH_3	87
m-NH_2	95
p-NH_2	63
m-NO_2	77
p-$CO_2C_2H_5$	83
o-Br	86
p-OCH_3	84
p-OH	38
m-OH	66
p-$COCH_3$	91
p-$NHCOCH_3$	77
p-CH=CHCH=CH_2	80
o-Biphenyl	93

Landesberg and co-workers[14] found that in the absence of the nitro compound reaction of $Fe_3(CO)_{12}$ and methanol affords a pyrophoric red solid whose physical properties resemble those of the hydridoundecacarbonyltriferrate anion. Addition of nitrobenzene to a solution of this hydrido species yields aniline.

The proton source for the reduction of the nitro group appears to be methanol. The oxygens of the nitro group ultimately appear in carbon dioxide and in the insoluble residues which result from the reaction.

Treatment of nitrobenzene with methanol free $Fe_3(CO)_{12}$ produces the complex shown in Figure 3 (18% yield), which was characterized by elemental analysis, and pmr, Mössbauer, and mass spectra. This compound is reminiscent of those prepared by Dekker and Knox[15] and Alper.[13] Evidence against involvement of a nitrene intermediate was presented. Two similar pathways rationalizing the reduction were presented. That pathway involving initial attack at a terminal carbonyl is presented in Scheme II; the second pathway involves initial attack at a bridging carbonyl.

The hydridoundecacarbonyltriferrate anion has also been found to effect the reduction of the carbon-nitrogen double bond in phthalazine and in a number of Schiff bases,[16] as well as the reduction of nitroxyl radicals to amines[17] in modest to good yields.

Formation of symmetrical disulfides from sulfenyl chlorides can be accomplished with iron pentacarbonyl in tetrahydrofuran below 0°C.[18]

Iron pentacarbonyl also catalyzes the cleavage of alkyl ethers by acid chlorides to alkyl chlorides and esters,[19] and has been found to effect certain transformations of steroidal dienes[20] such as the conversion of heteroannular steroidal dienes to their thermodynamically less stable homoannular isomers.

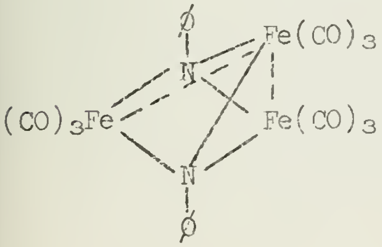
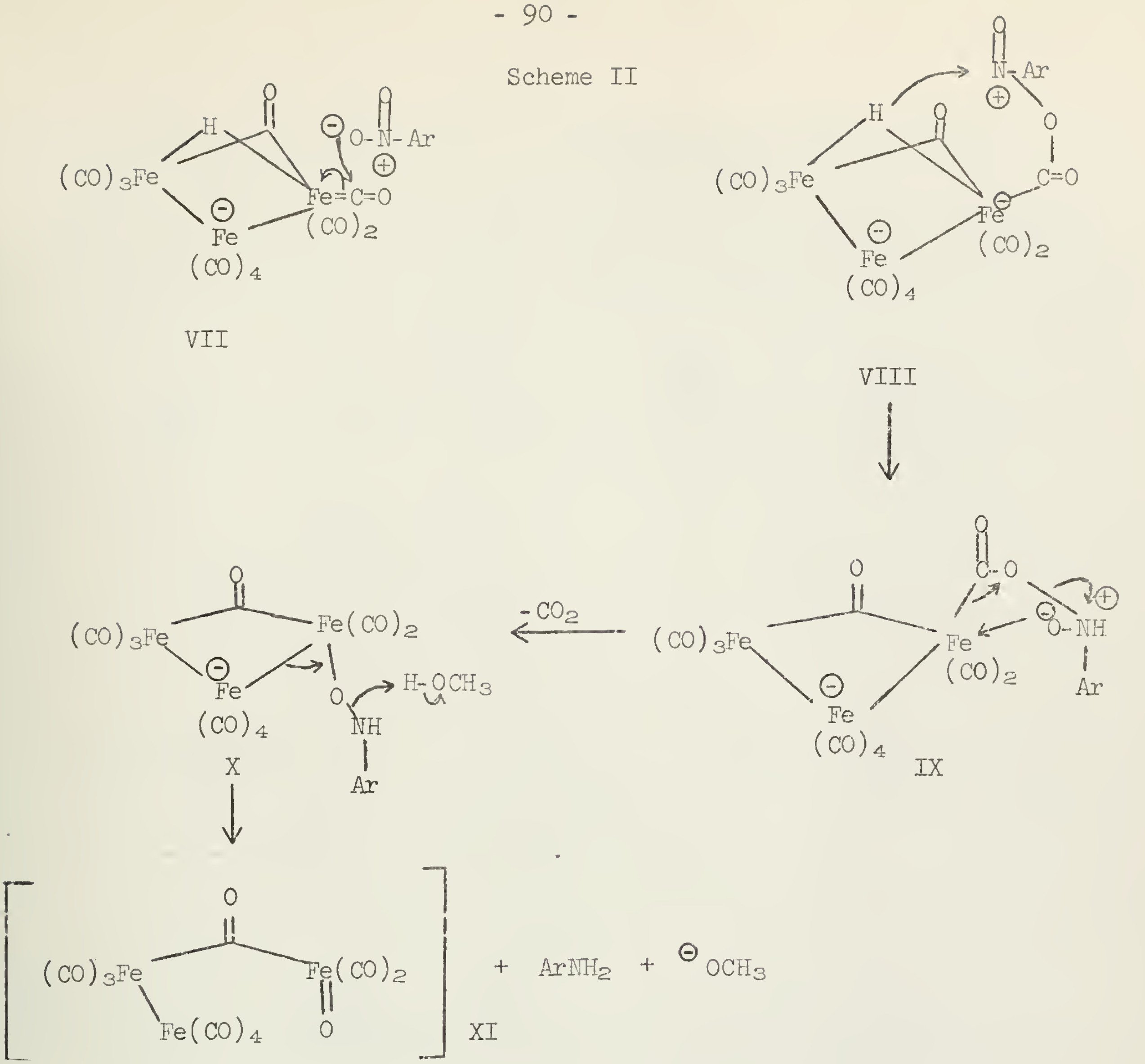


Figure 3

Scheme II



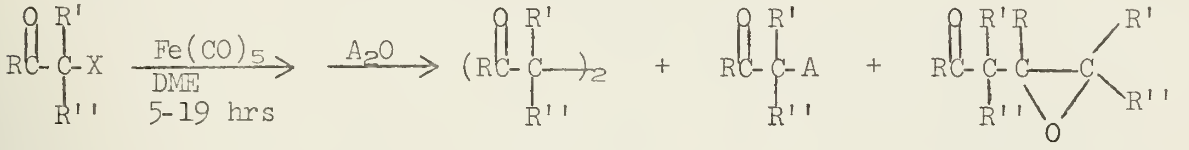
Recently Noyori and co-workers have described a method of hydrogenating the carbon-carbon double bond of α,β-unsaturated carbonyl compounds by adding the organic substrate to a mixture of iron pentacarbonyl, sodium hydroxide, and methanol.[21] An ether-water mixture can be substituted for methanol, and DABCO in moist DMF or HMPA can be substituted for the sodium hydroxide-methanol mixture. The yields for a wide variety of substrates are very good. No reductive coupling, skeletal rearrangements, or reactions of phenyl and furyl groups were observed. However, isolated double bonds, while they are not hydrogenated, positionally isomerize slowly. If deuterated solvents are used, each carbon in the α-β bond becomes deuterated. Although the exact nature of the reducing species is unknown, it was speculated that $[HFe_2(CO)_8]^-$ and $[HFe_3(CO)_{11}]^-$ might be responsible.

Tanabe and co-workers have found that iron pentacarbonyl can effect other useful reductions.[22] Enol acetates, vinyl chlorides, and α,β-unsaturated aldehydes are reduced to the corresponding olefin, while α-acetoxy ketones can be reduced to the corresponding ketone in a refluxing solution of butyl ether and iron pentacarbonyl under nitrogen. A 5-10 fold excess of $Fe(CO)_5$ is used. Yields are modest. Ketones, esters, and olefins remain unchanged. On the basis of their data a radical intermediate, which can abstract hydrogen from solvent is postulated to form after coordination and insertion of iron into the molecule.

CARBON-CARBON BOND FORMING REACTIONS

In 1961, Coffey found that iron pentacarbonyl converts diaryl dihalides to tetra-substituted ethylenes.[23] It was also noted that the reaction mixture passed through several highly colored stages.

Using Coffey's work as a starting point, Alper and Keung examined the reaction of a number of α-haloketones with iron pentacarbonyl in refluxing DME.[24] Three products were isolated after treatment of the reaction mixture with water as shown in equation (2). The distribution of products depended on the particular starting material.



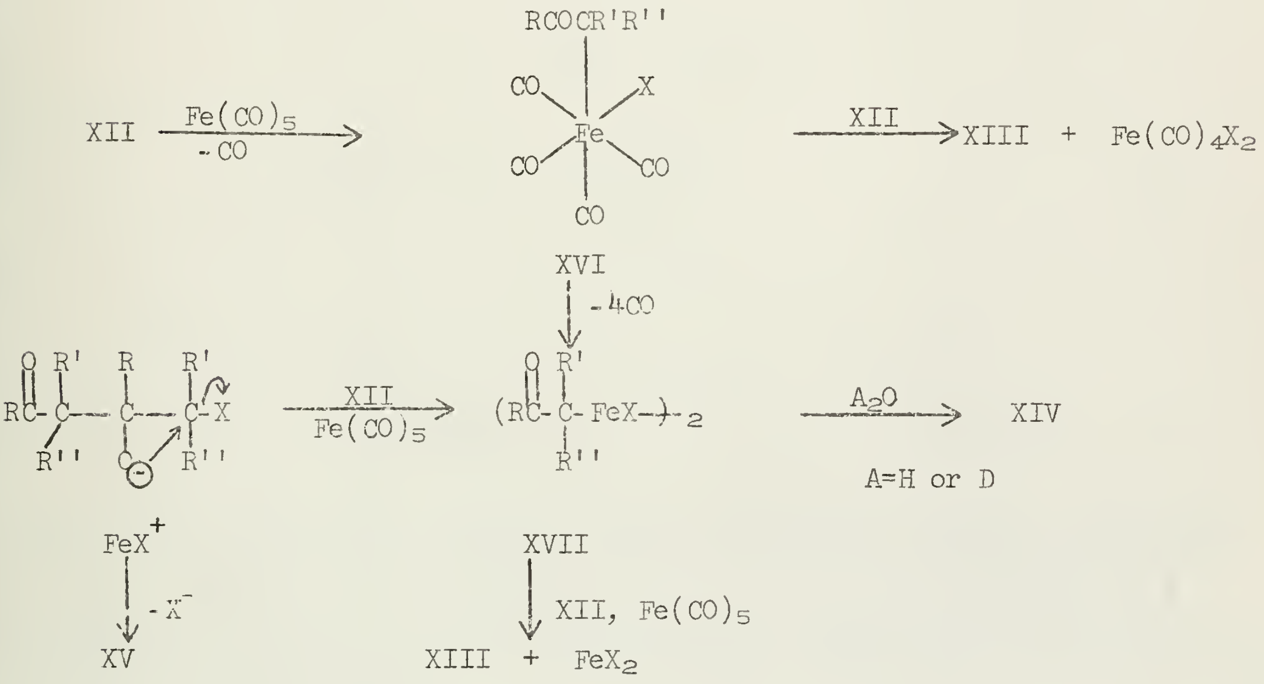
(2)

XII XIII XIV XV

A=H or D

A mechanism was proposed and is illustrated in Scheme III.

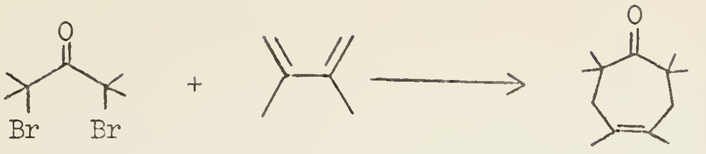
Scheme III



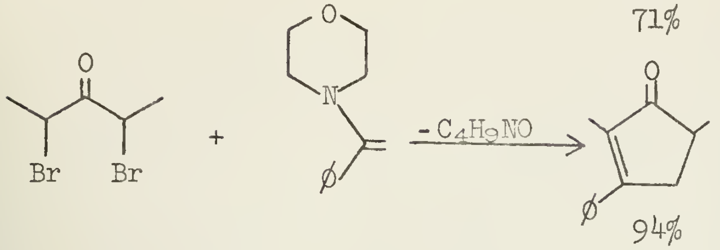
Complexes XVI and XVII were isolated by using the more reactive di-iron nonacarbonyl under milder reaction conditions. These complexes were characterized by a variety of physical methods, and their place in the above mechanism was shown. A radical mechanism was also considered. With this scheme established, the authors showed how it could be used to explain the products obtained from the interaction of sulfonyl chlorides and gem-dihalides with iron pentacarbonyl.

Noyori and co-workers have effected a number of apparent cycloaddition reactions between α,α'-dibromo ketones and 1,3-dienes,[25] eneamines,[26] aromatic olefins,[27] furans,[28] and carboxamides[29] in the presence of di-iron nonacarbonyl. Some illustrative examples follow. In all of these cases α,α'-dibromoacetone failed to give the desired products; α,α'-dibromo methyl ketones also failed to give the desired reaction.

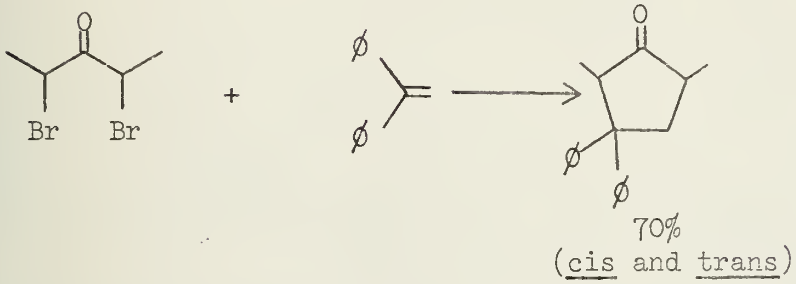
The products derived from equation (3) and (6) can be used as precursors of troponoid compounds.[25, 30] Reactions of the type illustrated by equation (4) offer a route to spiro-fused ring systems and azulene derivatives.[26]



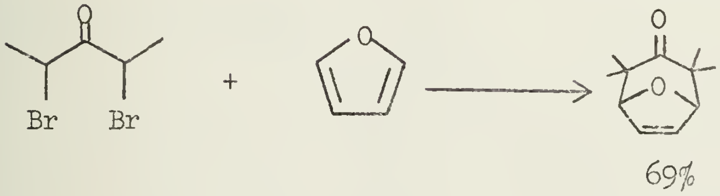
(3)



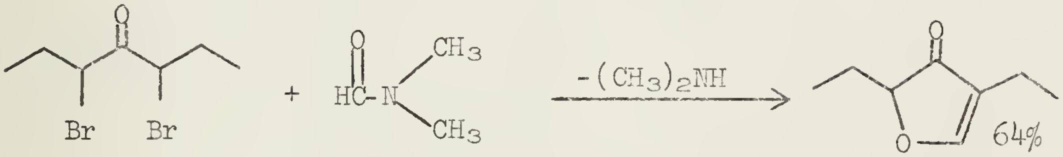
(4)



(5)



(6)



(7)

The procedure Noyori used to form dihydrofuranones (equation (7)) is a modification of the method Hoffman[31] used and appears to be more convenient. These furanones have been used as precursors of the muscarine alkaloids.[29]

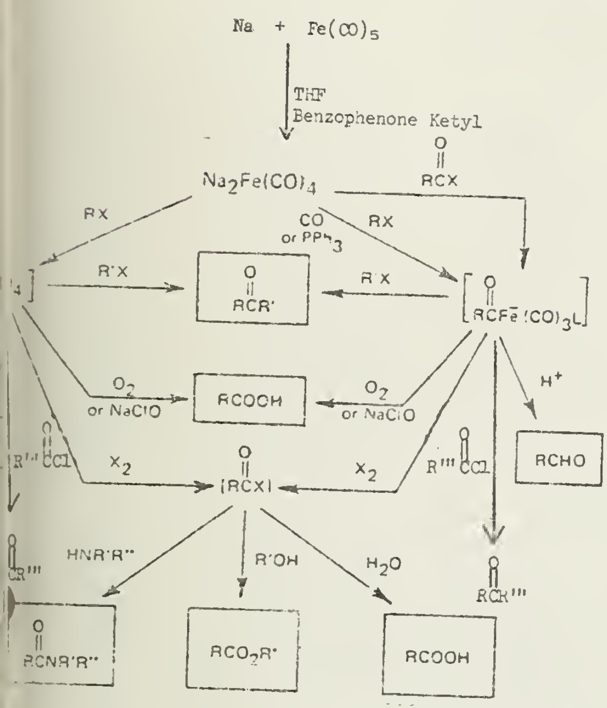
Mechanistic studies by Noyori, et. al. have provided evidence for the intermediacy of an iron enolate complex which is converted to an oxyallyl zwitterionic-Fe(II) complex. It is the latter intermediate which is considered to be the reactive species.

Sodium tetracarbonylferrate (-II) has been shown by Collman and co-workers to be such a useful reagent in organic synthesis[33] that the Ventron Corporation has recently made the reagent available commercially. Watanabe and his group have also realized the utility of this reagent.[34]

The synthetic usefulness of "Collman's Reagent" is shown in Scheme IV,[35] and the proposed mechanism is illustrated in Scheme V. Support for this proposal, which includes several fundamentals of organotransition-metal chemistry such as oxidative addition, migratory insertion, and reductive elimination,[36] is provided by the isolation of intermediates XVIII and XIX as their salts and their conversion to aldehydes and ketones.[37] Ion paring is believed to play a role in the rate of alkyl migration.[38]

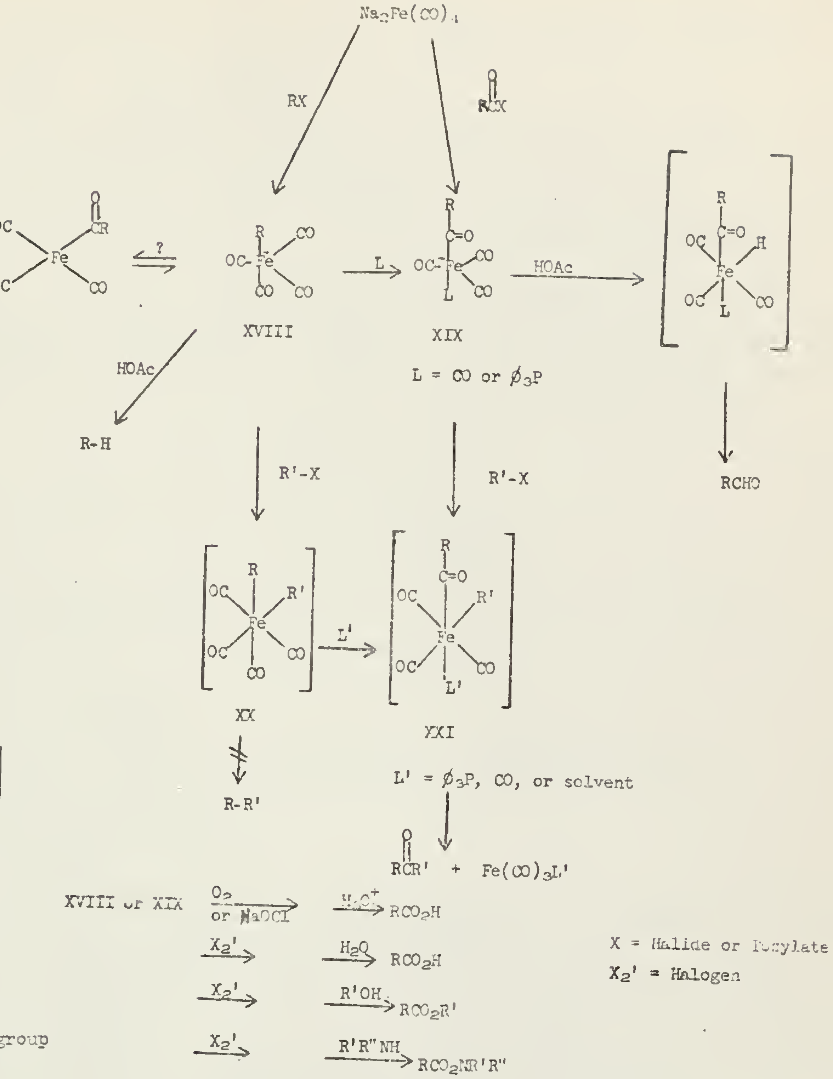
The synthetic utility of "Collman's Reagent" lies in the high yield of products and the inclusion of unprotected funtional groups such as -CHO, -CO$_2$R, -COR, -CN, -Cl, -NH$_2$, and -OH in the organic substrates. Some disadvantages

Scheme IV



R''' = perfluoroalkyl group
L = CO or ϕ3P

Scheme V



include competing elimination when secondary alkylating reagents are used particularly cyclohexyl groups, and the necessity of using excess alkylating agent for attachment of the second organic group to afford maximum yields.

Finally, mention might be made of some reactions similar to those carried out by the Collman group and which might be related to Noyori's work with α,β-unsaturated carbonyl compounds. For example, potassium hydridotetracarbonylferrate (-II) treated with ethyl acrylate under an atmosphere of carbon monoxide followed by treatment with iodine and ethanol gives diethyl methylmalonate and traces of diethyl succinate.[39] If ethyl crotonate or ethyl 3-butenoate are used as starting ester the products are diethyl ethylmalonate, diethyl methylsuccinate, and diethylglutarate in both cases. A mechanism which allowed for acyl iron carbonyl intermediate equilibration was proposed.

CONCLUSION

As has been seen, the iron carbonyls are able to effect some novel functional group transformations and carbon-carbon bond formations. More detailed mechanistic studies remain to be done. The complete utility of the iron carbonyls in organic synthesis remains to be realized.

BIBLIOGRAPHY

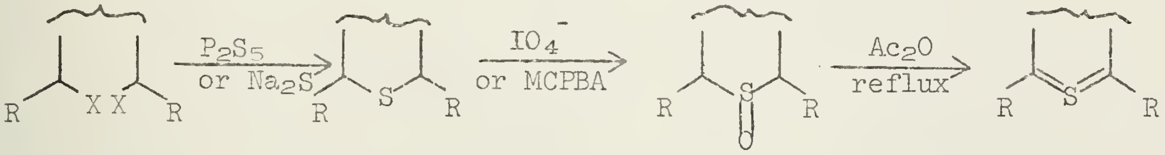
1. G. G. Buckley and N. H. Ray, J. Chem. Soc., 1154 (1949); A. F. M. Iqbal, Helv. Chem. Acta, *55*, 798 (1972); A. F. M. Iqbal, Tetrahedron Lett., 3385 (1971); J. E. Kmiecik, J. Org. Chem., *30*, 2014 (1965).
2. G. M. L. Cragg, J. Chem. Educ., *46*, 794 (1969).
3. F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Interscience Publishers, New York, N. Y., 1966, p 790.
4. E. W. Abel and F. G. A. Stone, Quart. Rev. (London), 23, 325 (1969); E. W. Abel and F. G. A. Stone, *ibid.*, *24*, 498 (1970) and references cited therein.
5. I. Wender and P. Pino, Eds., "Organic Synthesis via Metal Carbonyls," Vol. I, Interscience Publishers, New York, N. Y., 1968; M. Ryang and S. Tsutsumi, Synthesis, 55 (1971); M. Ryang, Organometal. Chem. Rev. A, *5*, 67 (1970); H. Alper, Organometal. Chem. Syn., *1*, 69 (1970); H. Alper, J. Org. Chem., *38*, 64 (1973).
6. H. Alper and J. T. Edward, J. Org. Chem., *32*, 2938 (1967).
7. H. Alper and J. T. Edward, Can. J. Chem., *48*, 1543 (1970).
8. A. Tanaka and J. P. Anselme, Tetrahedron Lett., 3567 (1971).
9. H. Alper and J. T. Edward, Can. J. Chem., *46*, 3112 (1968).
10. D. W. Chasar, J. Org. Chem., *36*, 613 (1971); H. C. Brown and N. Ravindran, Synthesis, 42 (1973) and references cited therein.
11. H. Alper and E. C. H. Keung, Tetrahedron Lett., 53 (1970).
12. H. Alper, *ibid.*, 1239 (1969).
13. H. Alper, Inorg. Chem., *11*, 976 (1972).
14. J. M. Landesberg, L. Katz, and C. Olsen, J. Org. Chem., *37* 930 (1972).
15. M. Dekker and G. R. Knox, Chem. Commun., 1243 (1967); for x-ray characterization see references cited in 13.
16. H. Alper, J. Org. Chem., *37*, 3972 (1972).
17. H. Alper, *ibid.*, *38*, 1417 (1973).
18. E. Lindner and C. Vitzthum, Angew. Chem. Int. Ed. Engl., *8*, 518 (1969).
19. H. Alper and J. T. Edward, Can. J. Chem., *48*, 1623 (1970).
20. H. Alper and J. T. Edward, J. Organometal. Chem., 14, 411 (1968); H. Alper and C. C. Huang, *ibid.*, *50*, 213 (1973).
21. R. Noyori, I. Umeda, and T. Ishigami, J. Org. Chem., *37*, 1542 (1972).
22. S. J. Nelson, G. Detre, and M. Tanabe, Tetrahedron Lett., 447 (1973).
23. C. E. Coffey, J. Amer. Chem. Soc., *83*, 1623 (1961).
24. H. Alper and E. C. H. Keung, J. Org. Chem., *37*, 2566 (1972).
25. R. Noyori, S. Makino, and H. Takaya, J. Amer. Chem. Soc., *93*, 1272 (1971).
26. R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, *ibid.*, *94*, 1772 (1972).
27. R. Noyori, K. Yokoyama, and Y. Hayakawa, *ibid.*, *95*, 2722 (1973).
28. R. Noyori, Y. Baba, S. Makino, and H. Takaya, Tetrahedron Lett., 1741 (1973).
29. R. Noyori, Y. Hayakawa, S. Makino, N. Hayakawa, and H. Takaya, J. Amer. Chem. Soc., *95*, 4103 (1973)
30. R. Noyori, S. Makino, and H. Takaya, Tetrahedron Lett., 1745 (1973).
31. H. M. R. Hoffman, K. E. Clemens, E. A. Schmidt, and R. H. Smithers, J. Amer. Chem. Soc., *94*, 3201 (1972).
32. R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi, and S. Tsutsumi, *ibid.*, *94*, 7202 (1972).
33. M. P. Cooke, Jr., *ibid.*, *92*, 6080 (1970); J. P. Collman, S. R. Winter, and D. R. Clark, *ibid.*, *94*, 1788 (1972); J. P. Collman, S. R. Winter, and R. G. Komoto, *ibid.*, *95*, 249 (1973); J. P. Collman and N. W. Hoffman, *ibid.*, *95*, 2689 (1973); J. P. Collman, R. G. Komoto, and W. O. Siegl, *ibid.*, *95*, 2389 (1973).
34. Y. Watanabe, T. Mitsudo, M. Tanaka, K. Yamamoto, T. Okajima, and Y. Takegami, Bull. Chem. Soc. Jap., *44*, 2569 (1971).
35. Ventron Corporation Brochure, "Collman's Reagent--Disodium Tetracarbonylferrate."
36. J. P. Collman, Accounts Chem. Res., *1*, 136 (1968).
37. W. O. Siegl and J. P. Collman, J. Amer. Chem. Soc., *94*, 2516 (1972).
38. J. P. Collman, J. N. Cawse, and J. I Brauman, *ibid.*, *94*, 5905 (1972).
39. H. Masada, M. Mizuno, and S. Suga, Bull. Chem. Soc. Jap., *43*, 3824 (1970).

SYNTHESIS AND PROPERTIES OF HETEROCYCLES CONTAINING TETRAVALENT SULFUR ATOMS

Reported by Kenneth Christy December 6, 1973

When Cava and Pollack discovered that 1,3-dihydrobenzo[c]thiophene 2-oxide could be dehydrated with refluxing acetic anhydride to benzo[c]thiophene, a method for generating tetravalent sulfur compounds was provided.[1] The usual method for the synthesis of tetravalent compounds is outlined in Scheme I. The conversion of sulfoxides to α-acetoxy sulfides (Pummerer reaction) is thought to proceed through an S-acetoxy ylide. The observed dehydration probably involves a 1,2 or 1,3 elimination of acetic acid from either an S-acetoxy ylide or an α-acetoxy sulfide intermediate. Phenyl lithium[2] and methylmagnesium bromide[3] have also been used to dehydrate the sulfoxide. In some cases treatment of the diketone with phosphorous pentasulfide gives the tetravalent sulfur compound directly.[4-9]

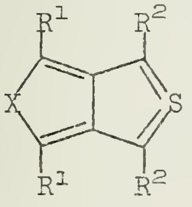
Scheme I



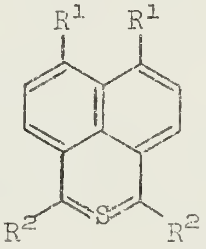
About half of the compounds reported have been isolated as high-melting deeply-colored crystalline products. The unstable tetravalent compounds have been trapped as N-phenylmaleimide, dimethyl acetylenedicarboxylate, or fumaronitrile adducts. The typical ions in the mass spectrum of the stable compounds are the molecular ion (as the base peak) and the doubly charged molecular ion. Schlessinger and Ponticello have concluded that a diamagnetic peripheral π-electron ring-current is present in acenaphtho[5,6-cd]thiopyran (11).[3] An X-ray crystallographic analysis of tetraphenylthieno[3,4-c]thiophene (3) has revealed relatively short C-S bond lengths and relatively long C-C bond lengths.[10] Although benzene solutions of N-methyl tetraphenylthieno[3,4-c]pyrrole (4) and 3 give no esr signal,[5,11] recent SCF-MO calculations, assuming no sulfur d-orbital participation, have predicted a triplet ground state for the unsubstituted thieno[3,4-c]pyrrole[12] and the unsubstituted thieno[3,4-c]thiophene.[13]

The common factor in the reactions of tetravalent sulfur compounds is the addition of the reagent to the carbons doubly bonded to sulfur. Hydrogenation over a platinum oxide or palladium on carbon catalyst occurs sluggishly to give the cis-sulfide.[2,4,5] Oxidation with either sodium dichromate or chromic acid produces the corresponding diketone.[4,5] In theory these tetravalent sulfur systems might undergo both acid-catalyzed and base-catalyzed addition reactions, but the elements of methanol have been added only under acid-catalyzed conditions.[5] When solutions of 6,7-dibromo-1,3-diphenylacenaphtho[5,6-cd]thiopyran (9) or 3 are irradiated in the presence of dissolved oxygen, photooxidation occurs to give the corresponding diketone.[2,5,14] In one instance a thermally labile thioozonide has been isolated and partially characterized.[14]

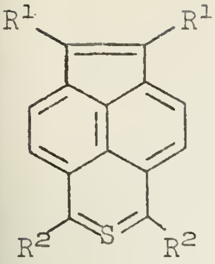
The synthesis of benzo[1]pleiadene-4,13-quinone has been achieved by trapping naphtho[1,8-cd]thiopyran (6) with 1,4-naphthoquinone.[15]



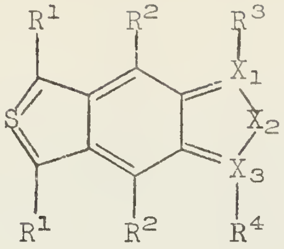
1, $X=S$; $R^1=CH_3$; $R^2=H$ (16,17)
2, $X=S$; $R^1=COOCH_3$; $R^2=H$ (16)
3, $X=S$; $R^1=R^2=C_6H_5$ (5,18)
4, $X=NH_3$; $R^1=R^2=C_6H_5$ (7,11)
5, $X=O$; $R^1=R^2=C_6H_5$ (11)



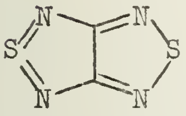
6, $R^1=R^2=H$ (15,19)
7, $R^1=-CH_2CH_2-$; $R^2=H$ (19)
8, $R^1=H$; $R^2=C_6H_5$ (22)



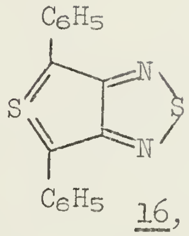
9, R^1=Br; R^2=C_6H_5 (2)
10, R^1=R^2=C_6H_5 (4)
11, R^1=R^2=H (3,20)



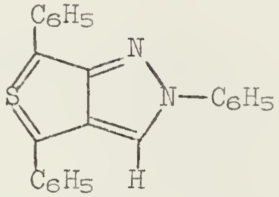
12, X_1=X_3=C; X_2=S; R^1=R^2=R^3=R^4=C_6H_5 (8)
13, X_1=X_3=N; X_2=S; R^1=C_6H_5; R^2=H (6)
14, X_1=C; X_2=NC_6H_5; X_3=N; R^1=R^2=C_6H_5; R^3=H (9)



15, (21)



16, (6)



17, (9)

BIBLIOGRAPHY

1. M. P. Cava and N. M. Pollack, J. Amer. Chem. Soc., 88, 4112 (1966).
2. I. S. Ponticello and R. H. Schlessinger, ibid., 90, 4190 (1968).
3. I. S. Ponticello and R. H. Schlessinger, Chem. Commun., 1214 (1969).
4. J. M. Hoffman, Jr., and R. H. Schlessinger, J. Amer. Chem. Soc., 91, 3953 (1969).
5. M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, ibid., 95, 2561 (1973).
6. J. D. Bower and R. H. Schlessinger, ibid., 91, 6891 (1969).
7. K. T. Potts and D. McKeough, ibid., 95, 2749 (1973).
8. K. T. Potts and D. McKeough, ibid., 95, 2750 (1973).
9. K. T. Potts and D. McKeough, ibid., 94, 6215 (1972).
10. M. D. Glick and R. E. Cook, Acta Crystallogr., Sect. B, 28, 1336 (1972).
11. M. P. Cava and M. A. Sprecker, J. Amer. Chem. Soc., 94, 6214 (1972).
12. L. Klasinic and N. Trinajstic, Tetrahedron, 27, 4045 (1971).
13. D. T. Clark, ibid.. 24, 2567 (1968).
14. J. M. Hoffman, Jr., and R. H. Schlessinger, Tetrahedron Lett., 797 (1970).
15. M. P. Cava, N. M. Pollack, and D. A. Repella, J. Amer. Chem. Soc., 89, 3640 (1967).
16. M. P. Cava, N. M. Pollack, and G. A. Dieterle, ibid., 95, 2558 (1973).
17. M. P. Cava and N. M. Pollack, ibid., 89, 3639 (1967).
18. M. P. Cava and G. E. M. Husbands, ibid., 91, 3952 (1969).
19. R. H. Schlessinger and I. S. Ponticello, ibid., 89, 3641 (1967).
20. R. H. Schlessinger and I. S. Ponticello, Tetrahedron Lett., 4057 (1967).
21. M. Carmack, R. W. Street, and R. Y. Wen, 158th National Meeting of the American Chemical Society, New York, N.Y., Sept., 1969. Abstract ORGN-54.
22. R. H. Schlessinger and A. G. Schultz, J. Amer. Chem. Soc., 90, 1676 (1968).

CARBANION REARRANGEMENTS: 1,2 SHIFTS AND ω-OLEFIN CYCLIZATIONS

Reported by Patricia L. Cavender December 10, 1973

INTRODUCTION

Organometallic compounds are valuable synthetic reagents but little is known about their exact character-carbanionic or covalent. It has been generally assumed that organomagnesium and organolithium compounds are more covalent than their sodium or potassium counterparts, but all have some carbanionic and possibly some radical character. Thus when rearrangements are observed, it is difficult to ascertain the mechanism. Part of this problem comes from the methods used to generate the anion in question. Alkyl halide plus metal, as in the Grignard, was among the first methods used. Ether cleavage by an alkali metal is also common. Still another method is the removal of a proton by an alkali metal or by a strong base such as potassium amide in ammonia. A second problem always encountered is that the mechanism for a given rearrangement may change drastically with relatively minor changes in structure.

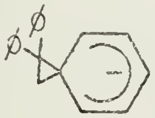
The mechanisms for many of the rearrangements presented here are merely speculative. It is thought that the predominant species are at least carbanion-like. Some are known to be anions since the effects of various types of delocalization- spiroaromaticity, homoaromaticity, and bicycloaromaticity- are reflected in the nmr and in the kinetic acidity of the compound.

This seminar will survey the recent work on two carbanion rearrangements; 1,2 alkyl or aryl shifts and ω-olefin cyclizations.

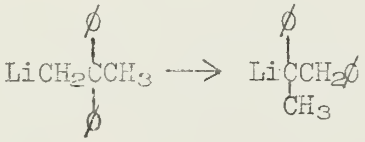
1,2 SHIFTS

Although carbonium ion rearrangements of this sort are well known, the analogous carbanion rearrangements involving carbon-carbon migrations are rare. The Grovenstein-Zimmerman rearrangement, reported independently in 1957 by Grovenstein and Zimmerman, is the most famous example.[1] They observed that when ϕ_3CCH_2Cl and lithium, sodium or potassium reacted in refluxing dioxane, the product is $\phi_2CHCH_2\phi$. A spiroanion intermediate, 1, was postulated. To test this hypothesis, labelled benzyl lithium was allowed to equilibrate with $\phi CH_2C\phi_2CH_2Li$ in THF at temperatures ranging from -65° to 5°C. Both the recovered benzyl lithium and the rearranged product, $\phi_2CHCH_2CH_2\phi$, were radioactive although a radiochemical equilibrium had not been established. These results point to an elimination-addition mechanism for this reaction. When the experiment was reported using labelled phenyl lithium and ϕ_3CCH_2Li, the compound in which the rearrangement had been originally observed, no labelled phenyl lithium was incorporated indicating either an intramolecular rearrangement or a cage effect.[2]

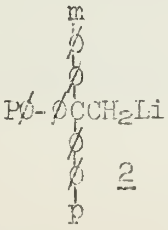
The Grovenstein-Zimmerman rearrangement has been observed in other systems, always with phenyl migration. (Equations 1 and 2) In the reaction depicted in Equation 3, the first rearrangement observed on the hydrocarbon rather than the chloride, no olefin is detected nor does the corresponding ofefin react under these conditions.[3]



1

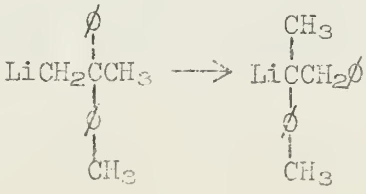


$$LiCH_2\underset{\phi}{\overset{\phi}{C}}CH_3 \longrightarrow Li\underset{CH_3}{\overset{\phi}{C}}CH_2\phi \qquad (1)$$



$$P\phi\text{-}\phi\underset{\underset{\underset{p}{\phi}}{\phi}}{\overset{\overset{\overset{m}{\phi}}{\phi}}{C}}CH_2Li$$

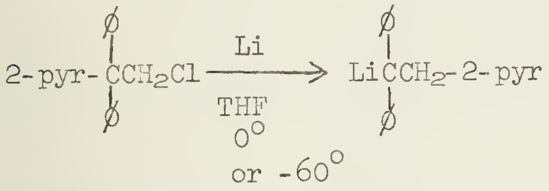
2



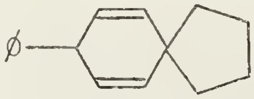
$$LiCH_2\underset{\underset{CH_3}{\phi}}{\overset{\phi}{C}}CH_3 \longrightarrow Li\underset{\underset{CH_3}{\phi}}{\overset{CH_3}{C}}CH_2\phi \qquad (2)$$

$$\phi_3CCH_2\phi \xrightarrow{\phi Na} \phi_2CHCH\phi_2 \qquad (3)$$

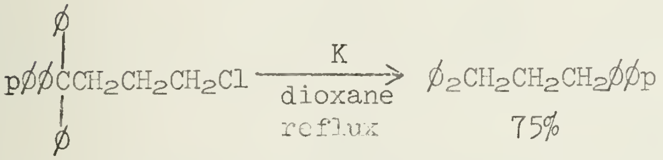
In order to gain more information about the mechanism of this rearrangement, studies to determine the order of preferred migration of various substituents were begun. It was found that in 2, the para biphenyl migrates 50 times more often than the meta biphenyl substituent. This indicates that electron withdrawers enhance the tendency to migrate and support the spiroanion transition state, 1.[4] Using pyridine, roughly equivalent to a para-nitrophenyl group, one would expect a 2-pyridyl substituent to migrate more readily than a 4-pyridyl substituent, and both to migrate more readily than a phenyl group. As can be seen in Equation 4, the 2-pyridyl does migrate. However, 4-pyridyl does not. A strong esr signal was observed during this reaction so a radical mechanism is currently being investigated.[5] Results on the reaction of ϕCMe_2CH_2Cl and lithium in THF at -65° also indicate a radical mechanism.



$$\text{2-pyr-}\overset{\phi}{\underset{\phi}{C}}CH_2Cl \xrightarrow[\text{THF, } 0^\circ \text{ or } -60^\circ]{Li} Li\overset{\phi}{\underset{\phi}{C}}CH_2\text{-2-pyr} \qquad (4)$$



3

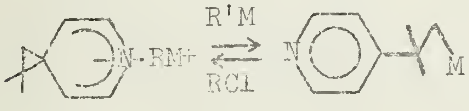


$$p\phi\phi\overset{\phi}{\underset{\phi}{C}}CH_2CH_2CH_2Cl \xrightarrow[\text{dioxane, reflux}]{K} \phi_2CH_2CH_2CH_2\phi\phi p \qquad (5)$$

75%

Recently Grovenstein has reported some 1,4 migrations. (Equation 5) In $\phi_3CCH_2CH_2CH_2Cl$, however, rearrangement accounts for less than 10% of the products. Concrete evidence for an intramolecular rearrangement exists since 1-biphenylbutane and 3 were isolated in equal amounts from the reaction of 1-chloro-4-biphenylbutane with Cs-K-Na eutectic at -70° in THF or with cesium or potassium in refluxing THF.[6]

A spiro anion was trapped by Fraenkel in an equilibrium similar to the one postulated in Equation 6. A strong electron withdrawer on nitrogen should stabilize the spiro form. The nmr of the deep red anion 4 indicated that there was little interaction between the cyclopropyl ring and the five member anion.[7] This system has 4n+2 π electrons and, according to the concept of spiroaromaticity, should not be especially stable. In fact, the hydrocarbon, spiro-[2.5]-octadienyl anion is not stable at -65°.



4

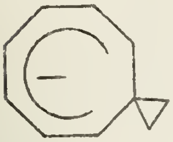
(6)

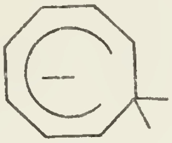
R' = nBu, Et
R = -COOEt
M = Li, Na, K, MgCl

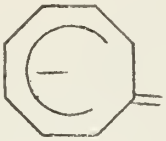
In essence, spiroaromaticity predicts that orbital overlap and delocalization can occur even when a saturated carbon intervenes if the "ribbon" of orbitals is connected to two other ribbons at its terminus. This system is aromatic when a cyclopropyl is fused with a ring containing 4 π electrons and will exhibit a diamagnetic ring current. This is best illustrated by the spiro[2.7]decatrienyl anion 5. The ring protons appear 0.6-0.8 ppm downfield due to the ring current compared to the analogous atropic dimethyl (6) or methylene (7) anions. The cyclopropyl protons in 5 appear at 1.50 ppm indicating that electron density is drawn out of the cyclopropyl ring and into the anion.[8]

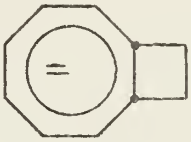
Anion 5, stable at -30°, rearranges in KNH_2/NH_3, undergoing a 1,2 alkyl shift to form the aromatic 10 π electron dianion 8.[9]

The [2.3] spiro system 9 has also been studied but no stabilization indicating spiroaromaticity was detected, possibly due to the electron-withdrawing chlorine substituents.[10]

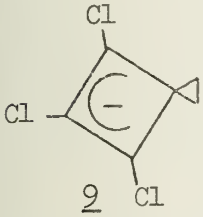

5


6

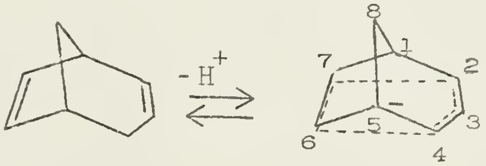

7


8

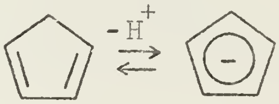
Homoaromaticity, where orbital overlap and delocalization occur due to the geometry of the system in spite of intervening saturated carbon atoms, can also stabilize certain anions. For example, the bicyclo[3.2.1] octadienyl anion 11, a biscyclopentadienyl anion, is a homologue of the cyclopentadienyl anion.



9

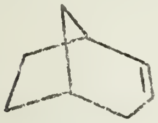


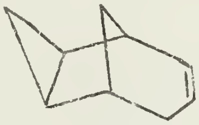
10 11

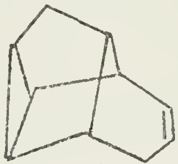


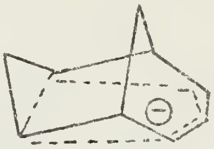
The rate of deuterium exchange in DMSO/KOtBu at 50°, a measure of the kinetic acidity of 10, is $10^{4.5}$ times faster than that of 12 and up to three deuterium atoms may be incorporated, indicating some interaction between the double bond and the allyl anion.[11] Further evidence of the aromatic character and the structure of this anion comes from the nmr. There is almost no change in the chemical shift of protons 1 and 5 upon ionization. (0.1 ppm) Delocalization of the negative charge shifts protons 6 and 7 2.25 ppm upfield. Protons 2 and 4 are 3.03 ppm upfield. From the upfield shift of the protons on C_8 (average 1.15 ppm) it can be calculated that between 30 and 40% of a cyclopentadienyl anion is present.[12]

In carbonium ion systems, the cyclopropyl ring is capable of delocalization comparable to that of a double bond. This does not appear to be true in carbanion systems. Deuterium exchange studies in DMSO/KOtBu of 13 and 14 showed no rate enhancement over 12, indicating that the delocalized form 15, the trishomopentadienyl anion, probably does not contribute significantly to the stability of this anion.[13]


12


13


14

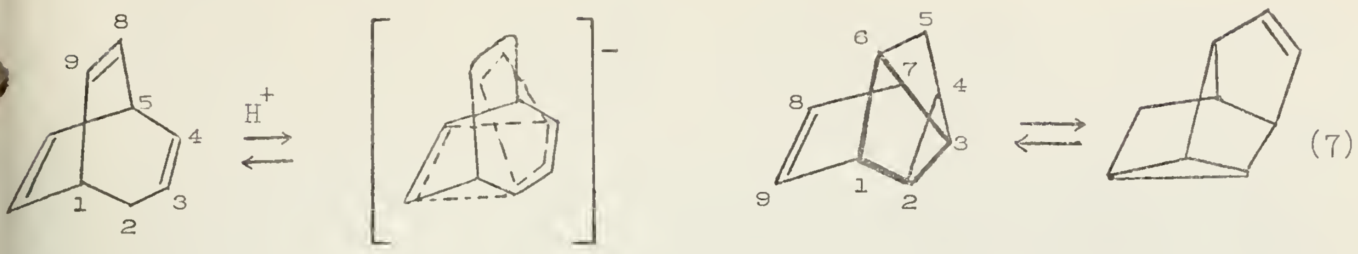

15

A third means of orbital overlap, bicycloaromaticity, predicts that the anion of bicyclo[3.2.2]nona-3,6,8-triene 16 should be capable of extensive delocalization as depicted in 17 and should be particularly stable.

In fact, the anions of 16 and of 18, tetracyclo.[$4.3.0.0^{2,4}.0^{3,7}$]nona-8-ene, are predicted to be completely degenerate $(CH)_9^-$ systems, similar to the well known $(CH)_9^+$ systems.

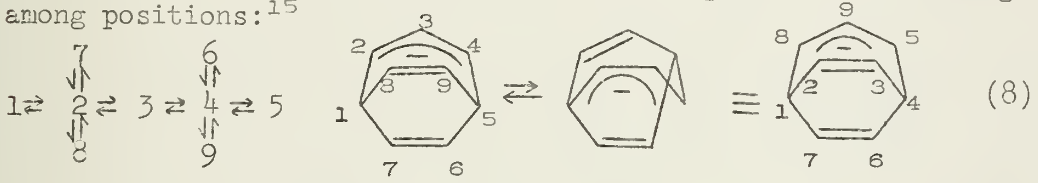
Upon hydrolysis of the 5-deutero Grignard of 18, Klumpp found deuterium scrambles to positions 4,5, and 6 (not separable by nmr) and to positions 8 and 9. This implies a degenerate rearrangement in which these carbons

become equivalent and those composing the marked five membered ring, 1,2,3,6, and 7, are also equivalent. (Equation 7)[14]

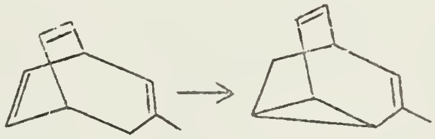


16 17 18

Deuterium in the 2 position of 16 completely scrambles after 2 days in Na/K alloy in DME or diglyme. The nmr is consistent with either a completely symmetrical anion or one that undergoes bridge flipping that is rapid on the nmr time scale. A series of 1,2 barbaryl type shifts are postulated. (Equation 8)[15] Evidence for this comes from Staley. In the reaction of 3-methyl-16 in KNH_2/NH_3 at 50° for three hours, methylbarbarlane 19 was isolated and 2.8 deuterium atoms were incorporated at a rate 750 times that of 10.[16] Grutzner also observed that the rates of deuterium incorporation of C_3 and C_6 are equal, giving further support to the barbarlane type rearrangement. This implies the following equivalence among positions:[15]



17

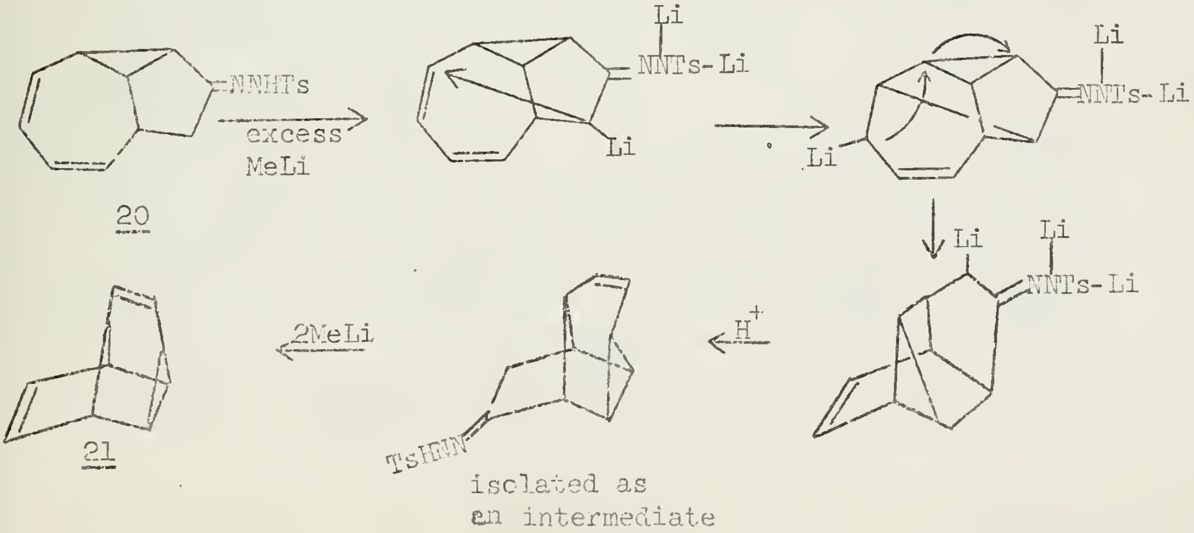


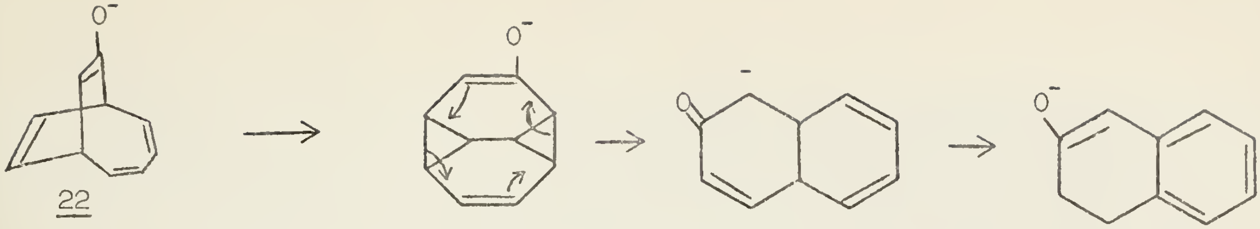
19

Rearrangements in the $(CH)_{10}^-$ system have also been observed. In the presence of excess methyl lithium, 20 rearranges to 21. (Scheme I) The mechanism proposed below assumes that the excess base metallates the tosyl group making it a poor leaving group and allowing cyclization to compete with elimination.[17]

A second $(CH)_{10}^-$ rearrangement has been observed on enolate 22 in KOtBu in DMSO or THF at temperatures ranging from 0° to 10°.[18] (Equation 9)

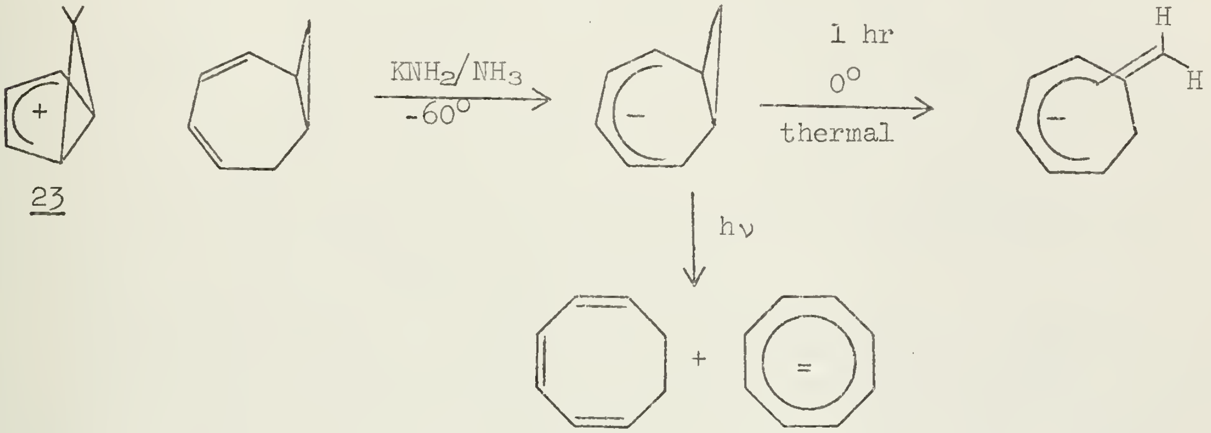
Scheme I





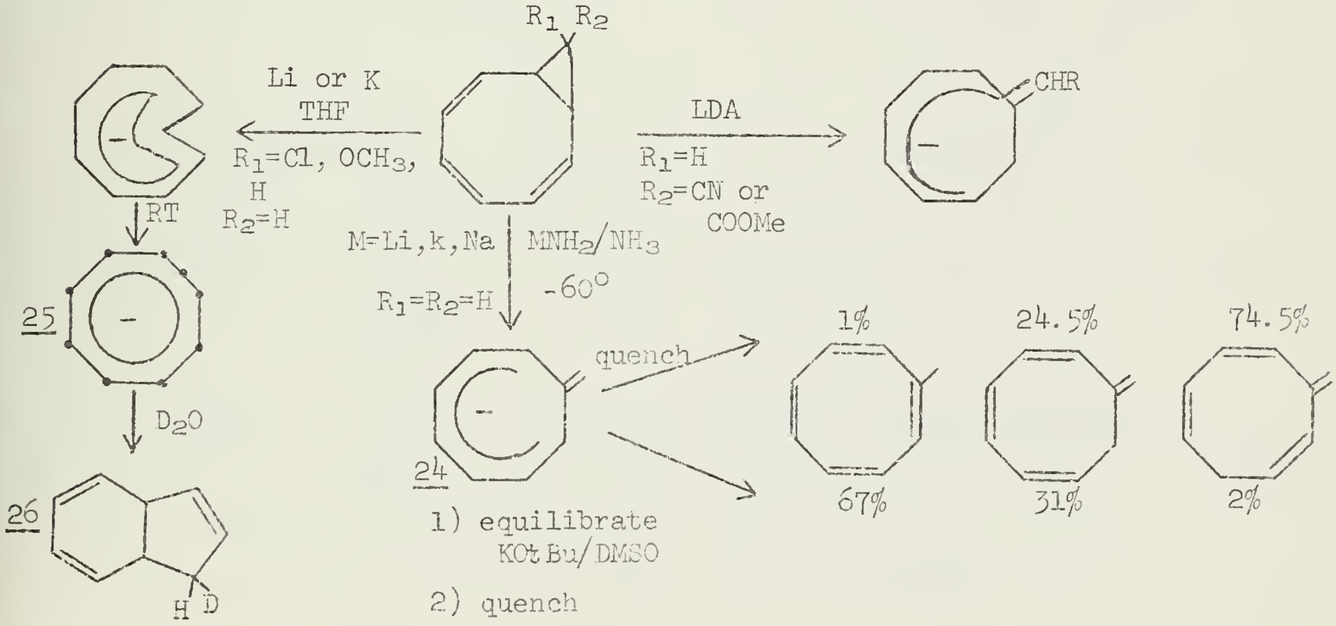
It has been observed that all positions in the five member ring of 23 are equivalent.[19] In the analogous anionic system, no such equivalence is observed. (Scheme II) There is, however, a disproportionation in the presence of light to give cyclooctatriene and cyclooctatetraene and dianion, a 10 π electron aromatic system.[20]

Scheme II



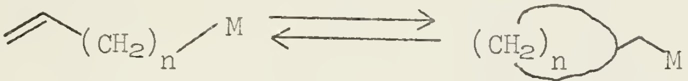
In the corresponding nine carbon system, different products are formed depending on the conditions used to generate and to quench the anion.[21] (Scheme III) It should be noted that 24 is a 4n+1 π electron system and should be atropic. The nmr indicates no ring current and no overlap with the exocyclic methylene even though the large coupling constant (J>10 Hz) of the ring protons implies that the system is very close to being planar.[21b] On the other hand, 25 has 10 π electrons and shows some aromatic character even though its tautomer, 26, is the only product of a D_2O quench.[21d]

Scheme III



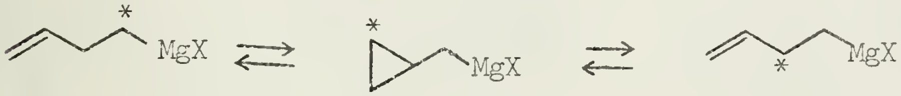
ω-OLEFIN CYCLIZATIONS

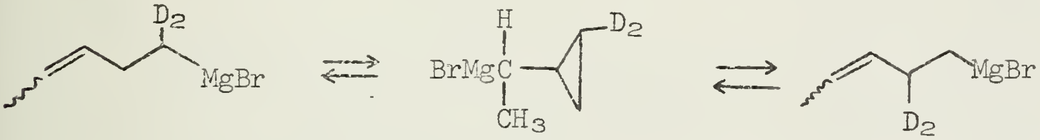
Another major rearrangement can be generalized as in Equation 10. It should be noted that this may be considered as an intramolecular addition of an organometallic to a terminal double bond. For n=2 or 3, the open or chain form is favored. For n=4 the cyclic form predominates and for n>4,


(10)

the arrangement is generally not observed. Other factors will also influence the position of the equilibrium. An increase in polarity for Mg<Li<Li-TMEDA favors cyclization as does going from a primary to a secondary organometallic. The rate at which the system comes to equilibrium is also influenced by the electronegativity of the metal (Li>>-MgR>-MgX) and by the structure of the compound (3°>2°>1°). However, other variables have opposite effects on the rate of rearrangement for Li and Mg compounds.[22] With increasingly polar solvents, the lithium rate increases, the magnesium rate decreases. In the presence of salts (LiOR or $MgBr_2$), the magnesium rate increases, the lithium rate decreases. These observations, coupled with the fact that the magnesium rate is concentration dependent, and that the lithium rate is independent of concentration, imply two different mechanisms, one for lithium and one for magnesium. Cyclopropyl carbinyl lithium may proceed through an ionization-recombination mechanism while that of the corresponding magnesium compound is probably concerted.[23]

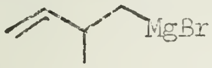
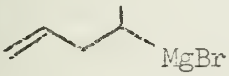
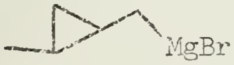
This rearrangement for n=2 may also be considered as a 1,2 shift of a vinyl group and was first observed by Roberts and coworkers in 1950.[24] (Equation 11) Later workers, using deuterium or carbon-14 labelled compounds, discovered that interconversion of the α ⇌ β positions, M=MgX or Li, is facilitated by phenyl or vinyl substituents in the α position. An equilibrium is probable since the same cis/trans ratio (21/79) is reached from either isomer.[25] (Equation 12) The reaction of n-heptaldehyde with the Grignards in Scheme IV gives the same products (27 and 28) although in different ratios according to the reaction conditions.[26]

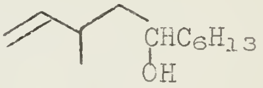

(11)

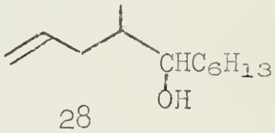

(12)

This rearrangement has also been observed in cyclic systems. It was first postulated by Roberts to explain the reaction depicted in Equation 13[24]

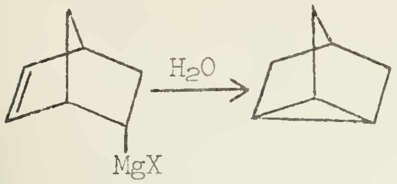
Scheme IV

Substrate	Solvent	Yield	Product
	Et_2O	63%	100% 27
	THF	62%	100% 27
	Et_2O	66%	100% 27
	THF	25%	10% 27, 90% 28
	Et_2O	40%	100% 27
	THF	59%	81% 27, 19% 28

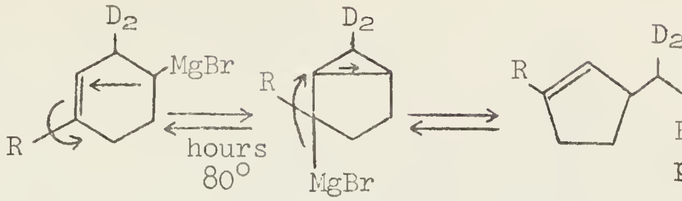

27


28

and has since been confirmed by Maercker (Equation 14) although the bicyclic intermediate has never been detected.[27]

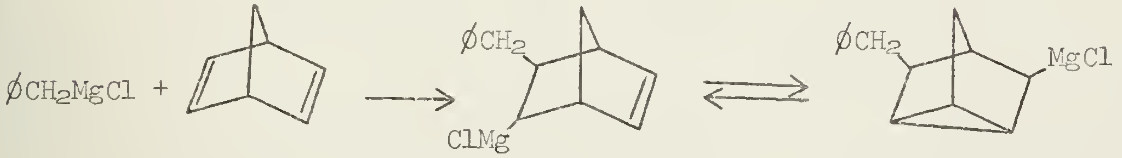


(13)

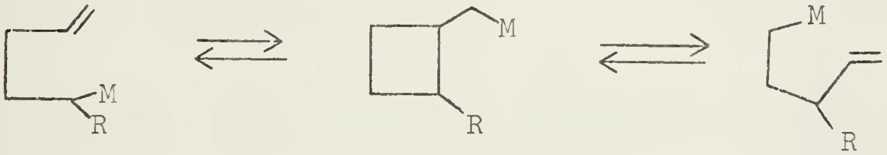


(14)
R=H,ϕ,
pϕCH_3, mϕCF_3

Lehmkuhl reports this rearrangement in the course of his investigation of Grignard addition to nonactivated double bonds.[28] (Equation 15)

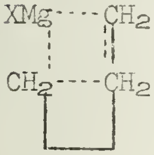


(15)

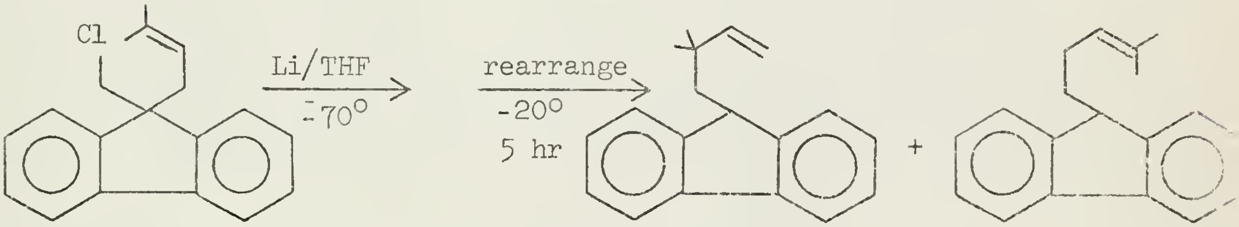


M=Li,Na,MgX
R=D_2 or -CH_3
(16)

The rearrangement for n=3 (Equation 16) may also proceed by several mechanisms. The reaction with M=Na is thought to be anionic in character, that with M=MgX to be four center or concerted, similar to 29.[29] A similar rearrangement, a 3,2 sigmatropic shift shown in Equation 17, has been described by Baldwin.[30]

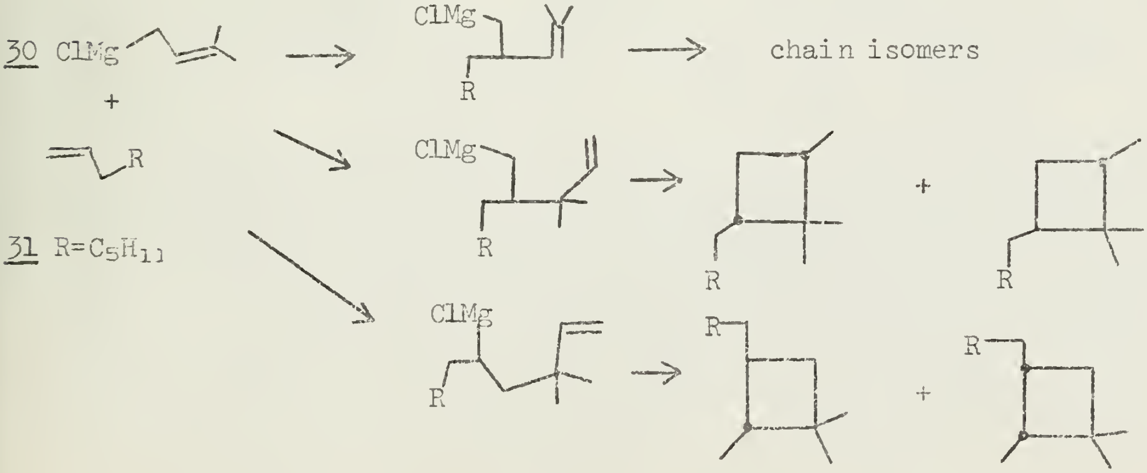


29

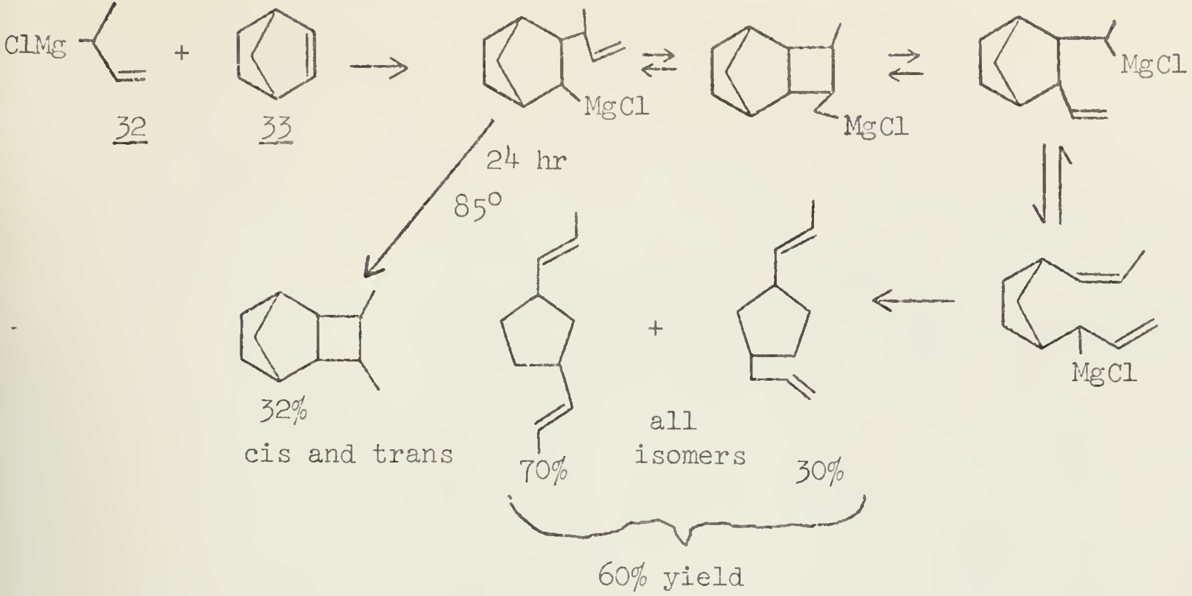


Lehmkuhl isolated cyclobutyl derivatives (41% of the total reaction mixture) in the addition of 30 to 31 due to a subsequent rearrangement. In the addition of 32 to 33, products explainable only by this rearrangement were isolated.[28] (Scheme V)

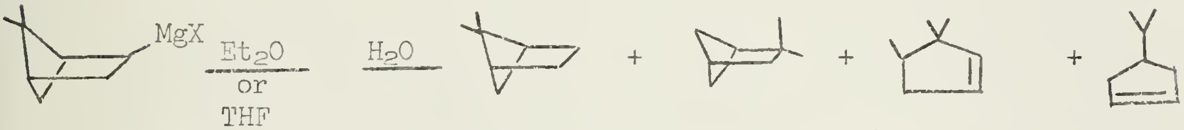
Scheme V



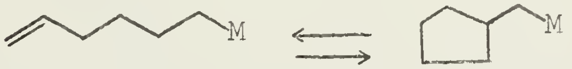
Scheme V (cont'd)



The same ring opening was observed by Hill in the bicyclo 2.2.1 hexyl ring system.[31] (Equation 18)

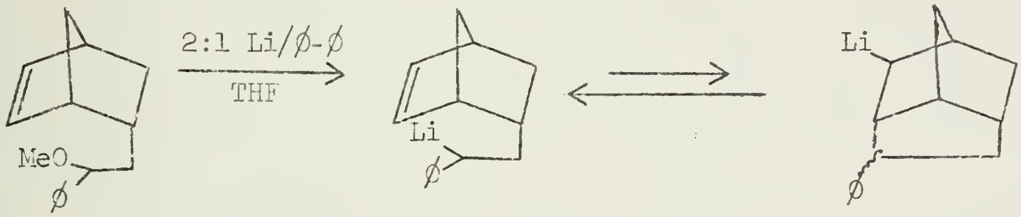


(18)

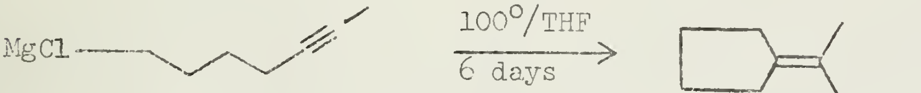


(19)

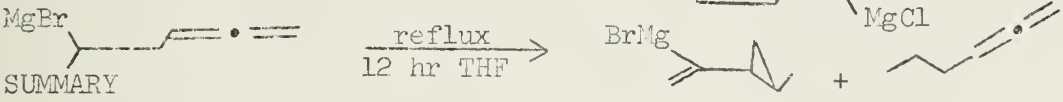
For n=4, (Equation 19) the cyclization from a terminal olefin to a cyclopentyl carbinyl metal derivative is quite a general one and has been observed for M=Li, MgX, AlR_3, Ga, and In. Conditions range from less than an hour at room temperature for M=Li in ether to three weeks at 110° neat for M=In.[32] Again, secondary compounds cyclize faster than primary. Trans compounds are the favored product. This rearrangement also has observed in cyclic systems.[33] (Equation 20) Terminal alkynes[34] and allenes[35] will also cyclize. (Equations 21 and 22)



(20)



(21)



(22)

SUMMARY

Carbanions may undergo 1,2 aryl and alkyl shifts. Spiroanions, reasonable mechanistic intermediates, may be particularly stabilized by spiroaromaticity as in the case of spiro[2.7]decatrienyl anion, 5. Carbanions may also exhibit homoaromaticity and bicycloaromaticity just as carbonium ions may. However, unless involved in spiroaromaticity, the cyclopropyl group is not equivalent to a double bond in delocalizing the negative charge. Degenerate rearrangements have also been observed. A second type of rearrangement is the facile cyclization-ring opening of terminal olefins and cycloalkylcarbinyl organometallics. It should again be noted that this rearrangement may also be considered as an intramolecular addition of an organometallic or carbanion to a terminal olefin.

BIBLIOGRAPHY

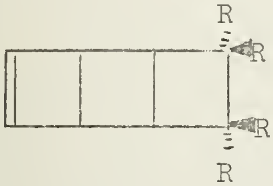
1. a) E. Grovenstein, J. Amer. Chem. Soc., 79, 4985 (1957); b) H. E. Zimmerman and F. J. Smentowski, ibid., 79, 5455 (1957).
2. E. Grovenstein and G. Wentworth, ibid., 89, 1852 (1967).
3. T. Crimmons, C. Hauser and W. Murphy, J. Org. Chem., 31, 4273 (1966).
4. E. Grovenstein, J. Amer. Chem. Soc., 94, 4971 (1972).
5. J. J. Eisch and C. A. Kovacks, J. Organomet. Chem., 25, C33 (1970).
6. E. Grovenstein, S. Akabori, and J. U. Rhee, J. Amer. Chem. Soc., 94, 4734 (1972).
7. G. Fraenkel, C. C. Ho, Y. Liang, and S. Yu, ibid., 94, 4732 (1972).
8. S. W. Staley, W. G. Kingsley, ibid., 95, 5804 (1973).
9. S. W. Staley, G. M. Cramer, and W. G. Kingsley, ibid., 95, 5052 (1973).
10. M. F. Semmelhack, R. DeFranco, and Z. Margolin, ibid., 95, 426 (1973).
11. J. M. Brown and J. L. Occolowitz, Chem. Commun., 376 (1965).
12. J. M. Brown, ibid., 638 (1967).
13. P. K. Freeman and T. A. Hardy, Tetrahedron Lett., 3939 (1971).
14. G. W. Klumpp, Rec. Trav. Chem., 87, 1053 (1968).
15. J. B. Grutzner and S. Winstein, J. Amer. Chem. Soc., 94, 2200 (1972).
16. S. W. Staley and D. W. Reichard, ibid., 91, 3998 (1969).
17. E. Vedejs and R. P. Steiner, Chem. Commun., 599 (1973).
18. M. J. Goldstein and S. A. Kline, Tetrahedron Lett., 1085 (1973).
19. R. F. Childs and S. Winstein, J. Amer. Chem. Soc., 90, 7146 (1968).
20. H. Kloosterziel and G. M. Gorter-LaRoy, Chem. Commun., 352 (1972).
21. a) G. Bocke and D. Martens, Angew. Chem. Int. Ed., 11, 724 (1972); b) S. W. Staley and G. M. Cramer, J. Amer. Chem. Soc., 95, 5051 (1973); c) T. J. Katz and P. J. Garrett, ibid., 86, 5194 (1964); d) P. J. Garrett and K. A. Knapp, Chem. Commun., 1215 (1970).
22. V. N. Drozd, Y. A. Ustynyuk, M. A. Tsel'eva and L. B. Dmitriev, J. Gen. Chem. Rus., 39, 1951 (1969).
23. A. Maercker and K. Weber, Ann., 756, 43 (1972).
24. J. D. Roberts and R. H. Mazur, J. Amer. Chem. Soc., 73, 2509 (1951).
25. A. Maercker and W. Streit, Angew. Chem. Int. Ed., 11, 542 (1972).
26. P. Miginiac and B. Cousseran, J. Organomet. Chem., 28, C5 (1971).
27. a) A. Maercker and R. Geuss, Chem. Ber., 106, 733 (1973); g) A. Maercker, P. Guthlein and H. W. Wittmayr, Ang. Chem. Int. Ed., 12, 774 (1973).
28. H. Lehmkuhl, D. Reinehr, J. Brandt and G. Schroth, J. Organomet. Chem., 57, 39, 49 (1973).
29. a) E. A. Hill and H. R. Ni, J. Org. Chem., 36, 4133 (1971); b) E. A. Hill and G. E. M. Shin, J. Amer. Chem. Soc., 95, 7764 (1973).
30. J. E. Baldwin and F. J. Urban, Chem. Commun., 165 (1970).
31. E. A. Hill, R. J. Theissen and K. Taucher, J. Org. Chem., 34, 3061 (1969).
32. J. St. Denis, T. Dolzine, and J. P. Oliver, J. Amer. Chem. Soc., 94, 8260 (1972).
33. P. K. Freeman, V. N. M. Rao, D. E. George and G. L. Fenwick, J. Org. Chem., 32, 3958 (1967).
34. H. G. Richey and A. M. Rothman, Tetrahedron Lett., 1457 (1968).
35. a) H. G. Richey and W. C. Kossa, ibid., 2313 (1969); b) M. Santelli and M. Bertrand, Comptes. Rend., C, 271, 757 (1970).

PHOTOADDITION REACTIONS OF BENZENE TO OLEFINS

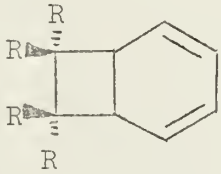
Reported by William F. Pfohl December 13, 1973

Photolysis of benzene in the gas or liquid phase at wavelengths above 2000Å has been reported to lead to isomerization products.[1-5] Among these are Dewar benzene, benzvalene, prismane, and fulvene. These and other valence bond isomers have been reviewed in a recent seminar.[6]

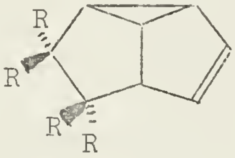
Irradiation of benzene in the liquid phase at 2537Å in the presence of olefins has been observed to yield cycloaddition adducts of types 1, 2, 3 and 4.[7-10] Adducts 1 and 2 stem formally from addition across the ortho positions while 3 and 4 result from formal additions across the meta and para ring positions, respectively.



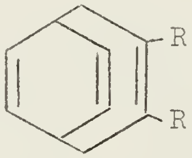
(1)



(2)



(3)



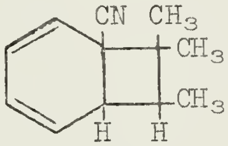
(4)

It has also been reported that 1,3 cycloaddition has occurred intramolecularly between the phenyl ring and olefinic substituent of 6-phenylhex-2-ene.[11,12]

In the past five years, there has been much theoretical consideration as to the nature of the reactive species involved in these reactions.[13-16] While it is known[17] that the reactive excited state of benzene is the singlet $^1B_{2u}$, (or some derivative of it) its geometry is not clear. This seminar will deal with some of these photocycloadditions reactions and the structure and stereochemistry of the products along with some of the proposals concerning the active species responsible for their formation.

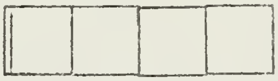
REACTIONS

Early reports[18,19] of photoaddition reactions of benzene and olefins describe 2 + 2 adducts. Photolysis of a solution of benzonitrile in 2-methyl-2-butene[20] produces adduct 5.



(5)

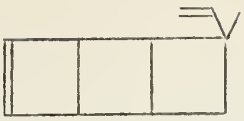
Srinivasan and Hill[21] report that the 2537 Å photolysis of a 20% benzene solution in cyclobutene gives adduct 6, an addition which formally appears to



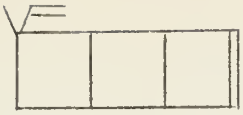
(6)

involve a Dewar benzene. The nmr shows the presence of two olefinic protons, δ5.75. Pyrolysis of 6 at 200° gives benzene and butadiene, identified by ultraviolet spectroscopy.

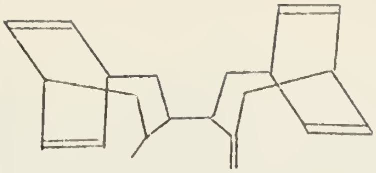
In 1966, Koltzenburg and Kraft[22] reported a series of photocycloadditions of various aromatic compounds with butadiene and isoprene. Upon irradiation of benzene and isoprene, they observed the formation of two stereoisomeric 1:1 adducts 7a and 7b as well as one 2:2 adduct 8.



(7a)



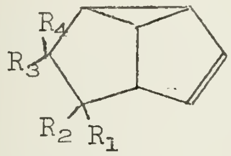
(7b)



(8)

Adduct 7 (bp 55° at 6 mm) was identified by comparison of its ir and nmr spectra to those obtained from the deuterated analog and by the use of proton decoupling experiments. Adduct 8 shows end absorption $\lambda_{max} 206 \epsilon 13,400$ and was characterized in a similar manner as 7. When the reactions were run in the presence of benzophenone, only dimers of the dienes were obtained indicating that addition occurs from an excited state of benzene.

Wilzbach and Kaplan[7] reported the formation of 1,3 adducts 9a, b, and c upon photolysis of a solution of benzene and cis-2-butene, cyclopentene, and 2,3-dimethyl-2-butene respectively. These adducts correspond to addition of the olefin across a cyclopropyl ring of benzvalene. The uv spectra of these adducts (λmax 200 ϵ 3000) were explained on the basis of a vinyl cyclopropane chromophare.[23] The C-H infrared absorptions, while not those



(9)

a) $R_1=R_3=CH_3$; $R_2=R_4=H$

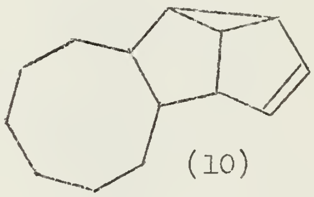
b) $R_1R_3=-(CH_2)_3^-$, $R_2=R_4=H$

c) $R_1=R_2=R_3=R_4=CH_3$

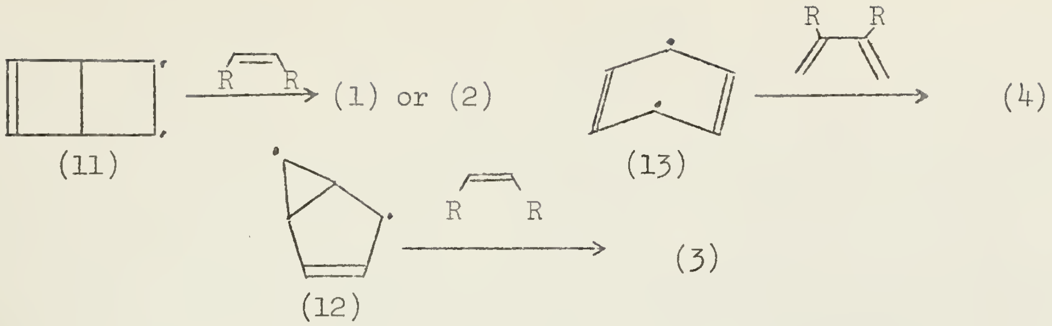
of a typical cyclopropane, are very similar to these of tricyclo [5.1.0.0.$^{4;8}$] oct-2-ene.[24] Nmr served to further positively identify the adducts.[7] These early reports of photocycloadditions of benzene to olefins are ones for which no stereochemical conclusions were drawn nor were any proposals concerning the identity of the excited intermediate.

THEORETICAL CONSIDERATIONS

In 1966, Bryce-Smith and co-workers[9] observed the addition of cis-cyclcöctene to benzene to give 10 in 85% yield. Benzophenone and acetone were found to be ineffective as photosensitizers. However, the rate of addition is increased two fold in the presence of β-propiolactone. The olefin inhibits the formation of fulvene but does not form an adduct when irradiated in a dilute solution of fulvene. A mechanism involving a diradical was proposed but the question of a triplet or singlet excited state was left open. Bryce-Smith and Longuet-Higgins[14] proposed several biradicals, 11, 12 and 13, which could lead to the observed ortho, meta, and para cycloaddition products which had been previously reported, shown in Scheme 1. They proposed that canonical structures 11 and 13 bear a close relationship to the triplet $^3B_{1u}$ state of benzene while 12 is similar to the singlet $^1B_{2u}$ state. The first step is excitation to the $^1B_{2u}$ state which can either react with olefins to give adducts of type 3 or undergo intersystem crossing to the $^3B_{1u}$ which can react to give adducts of type 1, 2 or 4.



(10)

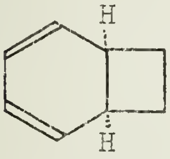


In 1969, Bryce-Smith[16] extended some orbital symmetry relationships for thermal and photochemical concerted cycloadditions to benzene. Although the Woodward-Hoffmann rules are not directly applicable to aromatic frameworks,[13] the relationships derived in Table 1[16] are in good agreement with the existing experimental results for cycloadditions of olefins to benzene.

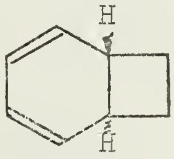
Table 1

	Addend	Addition Mode	Product	Excited Species		
				Addend	Benzene	
				(S_1,T_1)	B_{2u}(S_1)	B_{1u}(S_2,T_1)
1.	Ethylene	cis-ortho/cis-1,2-	14	A	F	A
2.	Ethylene	trans-ortho/cis-1,2	15	A	F	A
3.	Ethylene	meta/cis-1,2-	16	A	A	F
4.	Ethylene	para/cis-1,2-	17	A	F	A
5.	Ethylene	para/trans-1,2	17	A	A	A
6.	Cis-Butadiene	cis-ortho/cis-1,4	18	A	F	A
7.	Cis-Butadiene	meta/cis-1,4	19	A	A	F
8.	Cis-Butadiene	para/cis-1,4	20	A	F	A
9.	Cis-Butadiene	para/trans-1,4-	20	A	A	A
10.	Trans-Butadiene	para/cis-1,4-	21	A	A	A

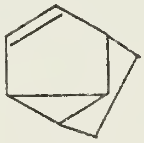
A=allowed, F=forbidden



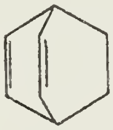
(14)



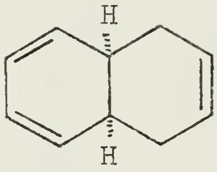
(15)



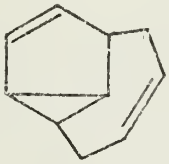
(16)



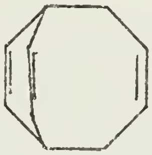
(17)



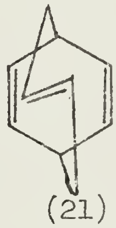
(18)



(19)



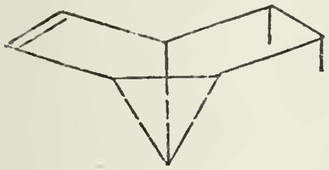
(20)

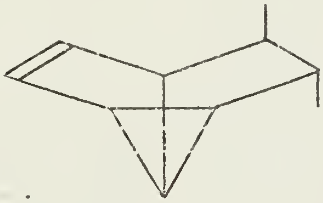


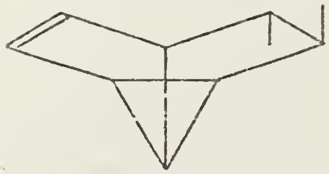
(21)

The suggestion that 12 is the precursor to both 1,3 addition and to benzvalene and fulvene formation[14] has raised some doubt. Wilzbach and Kaplan[5] found the yields of benzvalene and adduct formation have opposite wavelength dependencies. From this, they concluded that if there is a common intermediate, the ratio of the products would vary with its energy content. Morikawa and Cvetanovic,[27] studied the quenching of benzene fluorescence by hydrocarbons at high pressure, finding that monoölefins with a molecular weight greater than 2-butene show small but measureable quenching efficiencies. There is a probability that fluorescence quenching and adduct formation are related in that both involve the $^1B_{2u}$ state of benzene.

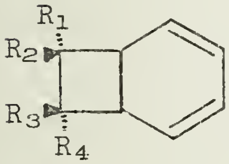
A kinetic study[25] of the cycloaddition of benzene to cis- and trans-2-butene showed that the rates of formation of adducts 22, 23, and 24 are proportional to the amount of light absorbed and to the pressure of cis- and trans-2-butene but are independent of benzene pressure. The additions are stereospecific which seems to indicate a singlet intermediate. However, a triplet biradical cannot be ruled out if ring closure occurs faster than rotation about the original double bond in the olefin. Oxygen is known to quench the excited singlet state of benzene strongly as does biacetyl. For oxygen, the rate constant for quenching of singlet benzene is $1.6\text{X}10^{-10}$ cc/molecule sec and for biacetyl $1.7\text{X}10^{-10}$ cc/molecule sec.[28] Morikawa and co-workers[25] found these rate constants to be in agreement with their values and observed a decrease in rate for adduct formation as well as for cis-trans isomerization of 2-butene. These results suggest the intermediacy of a singlet $^1B_{2u}$ benzene or singlet diradical as proposed by Bryce-Smith and Longuet-Higgins[14] which leads to adduct formation.


(22)

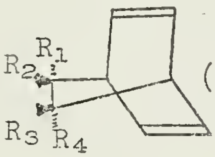

(23)


(24)

The photolysis of 5-10% solutions of benzene in cis- and trans-2-butene[3] produces 25a and 26a and 25b and 26b, respectively. Adducts 25 and 26 are formed with retention of stereochemistry at the olefin as found in the case of 1,3 additions.[7,25] These results imply that the reaction is concerted and that the products appear to be derived from a common precursor.[8] Until this time, 1,2 photoaddition had been observed only where the ethylenic compound was excited or where one of the reactants possessed marked acceptor properties[20] as pointed out in Table I.[16] Since there is good evidence[25] that 1,3 addition occurs from the $^1B_{2u}$ state of benzene, it is likely that this state is involved in 1,2 and 1,4-photoadditions as well, because the quantum yields of the various adducts remain constant over a wide range of concentrations and proportions, whereas the benzene singlet-triplet ratio would most likely vary.[8] It may be possible that formation of an excited complex from $^1B_{2u}$ benzene and ground state olefin, in which mixing of states occurs, results in relaxation of orbital symmetry restrictions. One could also invoke the formation of benzene-olefin exiplexes.



(25)

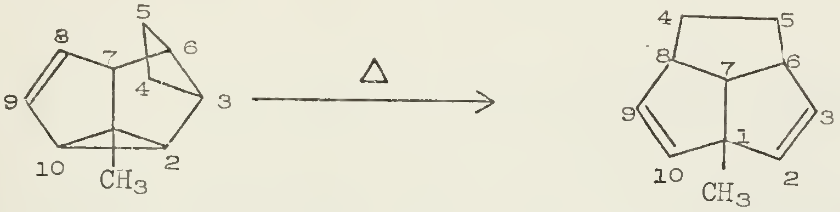


(26)

a) $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
b) $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$

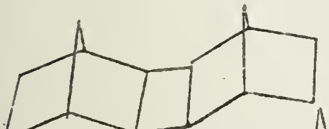
Srinivasan[17] suggested that the 1,3 addition of toluene and the xylenes to cyclobutene might provide a clue to the structure of the excited intermediate. The photolysis of toluene, p-xylene and o-xylene produce one major adduct each while m-xylene produces two. The stereochemistry of each adduct was easily established as 3,6-endo, since each undergoes the (2'vinylcyclopropane) cyclobutane rearrangement[26] shown in Scheme 2.

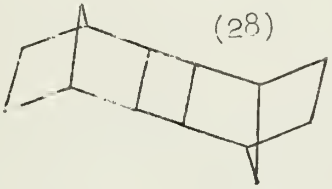
Scheme 2

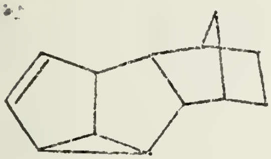


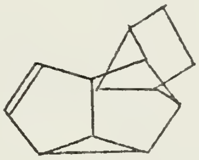
The nmr spectra of all five adducts show absence of absorption at δ 3.1 which is observed in the adducts of benzene and cyclobutene. This suggested that each of the xylene adducts has a common substituent at the 1 position. The preferential orientation of a methyl group[17] may be due to a strong directive influence from the methyl group or the intermediacy of an excited state in which the methyl substituent is in a certain position.

A study[29] of the photoaddition of norbornene to benzene seems to provide more insight as to the nature of the excited intermediate. There are two interesting features in using norbornene as the olefin. First, norbornene photodimerizes to give two products 27 and 28 with benzene acting as a photosensitizer.[30] This process is believed to involve the triplet of the olefin. It was proposed[29] that a quantitative study of the formation of 27 and 28 and the adducts would provide a way to examine competition between the reactions from excited triplet and singlet states assuming that adduct formation proceeds from the singlet state. Secondly, because of the strong directive influence of the bulky olefin to the cycloaddition, only two 1:1 adducts 29 and 30 are formed. Besides formation of 27 and 28, the major adduct was found to be 29 and the minor adduct 30. All other adducts formed amount to less than 1% of 29. The uv shows absorption λ max 220 typical of the vinyl cyclopropane chromophore. Adduct 30, when heated to 280° for 20 minutes is converted cleanly into 29 which is stable under these conditions. Srinivasan[29] suggested a possible mechanism shown in Scheme 3.


(27)


(28)


(29)


(30)

Scheme 3

$$B + h\nu \xrightarrow{k_2} B^1 \qquad 1$$
$$B^1 \xrightarrow{k_3} B^3 \qquad 2$$
$$B^1 + N \xrightarrow{k_4} A \qquad 3$$
$$B^1 \xrightarrow{k_5} B \qquad 4$$
$$N + B^3 \xrightarrow{k_6} B + N^3 \qquad 5$$
$$N^3 + N \xrightarrow{k_7} D \qquad 6$$
$$B^3 \xrightarrow{k_8} B \qquad 7$$
$$N^3 \xrightarrow{k_9} N \qquad 8$$

This scheme incorporates the $^1B_{2u}$ state for adduct formation and the $^3B_{1u}$ state for dimerization of the olefin. From the steady state approximation, equations 9 and 10 can be derived.

$$\Phi_A = \frac{1}{(k_3 + k_5)/k_4[N] + 1} \qquad 9$$

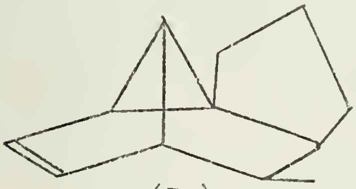
$$\Phi_D = \frac{k_3 k_6 k_7 [N]^2}{(k_7[N] + k_9)\ (k_6[N] + k_8)\ (k_3 + k_5 + k_4[N])} \qquad 10$$

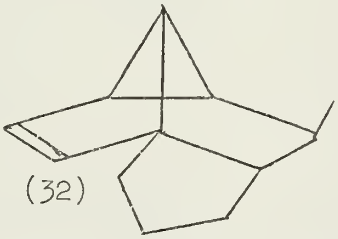
Φ_A and Φ_D are quantum yields for adduct and dimer formation respectively. Equation 9 suggests that a plot of $\frac{1}{\Phi_A}$ vs. $\frac{1}{[N]}$ should be linear with an intercept of 1. This was found to be the case within experimental error over a range (0.8 to 1.3M) of concentrations. Extrapolation of [N] to ∞, gave $\Phi_A = 0.52 \pm 0.12$. The quantum yield for adduct formation indicates that deactivation of B^1 (with no adduct formation) occurs in about one-half of the collisions. Equation 11 was found to be more quantitatively significant to the experimental trend of the ratio Φ_A/Φ_D.

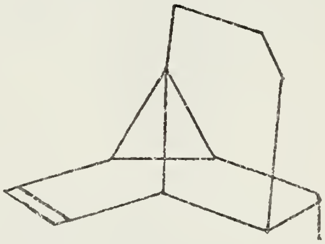
$$\Phi_A/\Phi_D = k_4(k_7[N] + k_9)(k_6[N] + k_8)/k_3 k_6 k_7 [N] \qquad 11$$

The experimental values for Φ_A/Φ_D for 1 to 8M solutions, fall on a parabola predicted by equation 11. This suggested that dimerization according to equation 6 is an inefficient process even at high norbornene concentrations.

Intramolecular 1,3 cycloadditions have been observed[11,12] in the 2537 Å photolyses of cis- and trans-6-phenylhex-2-ene in cyclopentane solutions. Initial excitation of phenyl group followed by intersystem crossing and energy transfer to the olefin was anticipated since it has been observed[31] in the analogous 1-phenyl-2-butene system leading to isomerization about the olefinic double bond. Although cis-trans isomerization was observed,[11,12] the major reaction product is a mixture of isomers resulting from 1, 3 internal cycloaddition. Cis-6-phenylhex-2-ene yields adducts 31 and 32 with a combined quantum yield of 0.25, while the trans-isomer yields adduct 33.


(31)

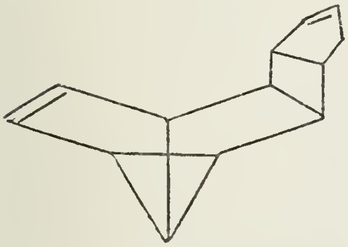

(32)

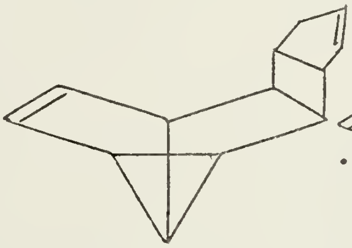

(33)

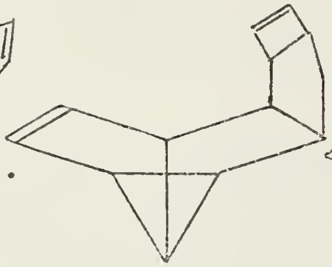
Several other pertinent observations were also made.[11] Oxygen quenchs the cycloaddition and fluorescence yields with equal effectiveness. The quantum yield for cis-trans isomerization is 0.05 compared to 0.16 for 1-phenyl-2-butene.[31] Finally, the relative fluorescence yields for toluene, 1-phenylhexane 1-phenyl-2-butene and 6-phenylhex-2-ene are 1.0, 0.96, 0.72, and 0.05, respectively. This result shows a pronounced limitation for the substrate which undergoes internal cycloaddition.

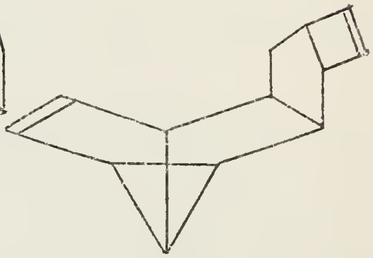
An alternate possibility to the diradical intermediate proposed by Bryce-Smith and Longuet-Higgins[14] is the formation of an exiplex which could go to products or, by dissociating to the ground state, might give rise to efficient internal fluorescence quenching.[11] This explanation is analogous to the exiplexes proposed to explain cycloaddition and fluorescence quenching of aromatics by dienes[32] and of ketones by olefins.[33] No proposal as to the nature of the exiplex was given.

Wilzbach and Kaplan[8] have also proposed the intermediacy of a complex between the excited singlet of benzene and the olefin. Two recent reports seem to support the idea of a highly symmetrical intermediate.[34, 35] Irradiation of a 15% solution of bicyclo [3.2.0] hepta-2,6-diene in benzene at 2537 Å produces four 1:1 adducts 34, 35, 36, and 37. Adducts 34 and 35 are obtained in 30% yield while 36 and 37 are obtained in 15% yield.

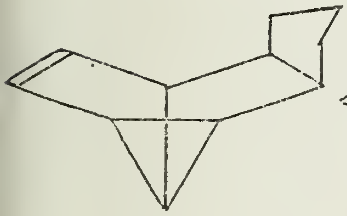

(34)

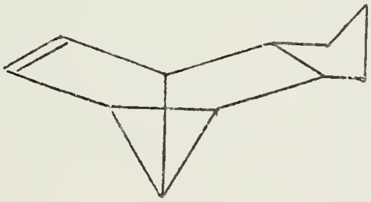

(35)


(36)

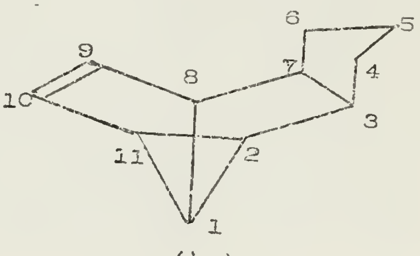

(37)

It should be noted that formation of only adducts 34-37 suggests the cycloaddition to be highly stereospecific since, considering the geometry at the point of addition, exo or endo, the orientation of the cyclobutane ring with respect to the cyclopentene ring, and the location of the methylene groups in the cyclopentene ring, there is a possibility of forming at least 16 stereoisomers. It should also be noted that 34 and 35 are interchangeable through the (2'-vinylcyclopropane) cyclobutane rearrangement.[26] Cornelisse, Merritt and Srinivasan[35] also observed that the cycloaddition of benzene to cyclopentene affords 38 and 39 in a 4:1 ratio. The intermediacy of a highly symmetric species such as benzene was proposed[35] since the $^1B_{2u}$ state of benzene is believed to retain the hexagonal structure of the ground state. Results which further support the proposal of a symmetric intermediate were presented by the 1,3 cycloadditions of toluene, p-xylene, o-xylene, m-xylene and mesitylene with cyclopentene. Adducts 40a, and b were formed from toluene and p-xylene 40c, and d from o-xylene, 40e and f from m-xylene and 40g and h from mesitylene.


(38)


(39)

Φ=0.16 from benzene and cyclopentene



(40)

a) 1-Methyl Φ=0.21
b) 1,10-Dimethyl Φ=0.13

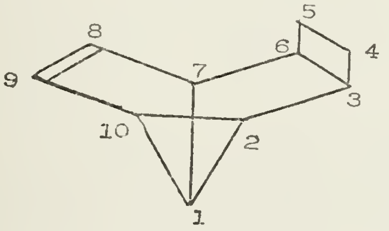
c) 1,8-Dimentyl
d) 1,2-Dimentyl } Φ=0.08

e) 1,9-Dimethyl
f) 1,11-Dimethyl } Φ=0.05

g) 1,9,11-trimethyl
h) 2,8,10-trimethyl } Φ=0.015

The quantum yields support the idea that a methyl group on the benzene ring has a definite activating effect on the ortho positions.[35] Benzene has six equivalent modes for 1,3 addition implying $\Phi=0.027$/mode. Toluene which has only one mode of addition has $\Phi=0.21$/mode. This also suggests a deactivating effect on the meta positions since the adduct corresponding to addition at C-3 or C-5 of toluene was not detected. Such adducts would have been observed if the quantum yield per mode were the same as benzene since the product formed would have been at least 1/8 of the observed adduct 40a.

A final possibility for the excited intermediate was proposed on the basis of the photoreactions of benzene and toluene with 1,2 and cis-3,4-dimethylcyclobutene.[35] On the basis of the quantum yields for adducts 41a, b and c, formation of an exiplex, figure 1, was found to be consistent with the experimental results.



(41)

a + b-1,2-dimethylcyclobutene
c-3,4-dimethylcyclobutene

a) 3,6-dimethyl $\Phi=0.10$
b) 1,3,6-trimethyl $\Phi=0.02$ Major adducts
c) 1,4,5-trimethyl $\Phi=0.11$

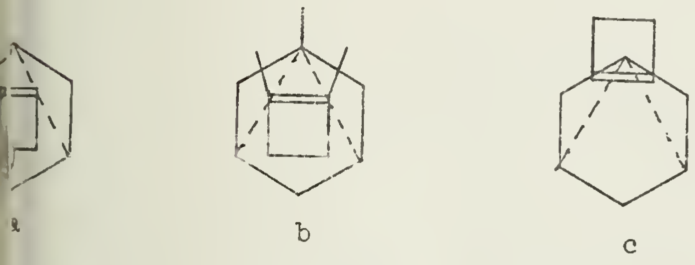


Figure 1

a) endo addition of benzene to cyclobutene
b) addition of toluene to 1,2-dimethylcyclobutene
c) exo addition of benzene to cyclobutene

The low value for the quantum yield of 41b may be explained on the basis of steric interaction between the methyl groups in figure 1b. Small ring olefins give almost exclusively endo adduct which suggests that maximum overlap between the bonds of the two rings, figure 1a, is most likely favored. As the olefin ring size increases, more exo adduct is formed since overlap may become less efficient.[29] Bonding between the aromatic nucleus and the olefin is concerted[8] and may be followed by puckering of the benzene ring and closure of the cyclopropane ring along either of the dotted lines in figure 1a,[35] resulting in adduct formation with retention of olefin configuration.

CONCLUSION

The formation of 1,3 adducts of benzene or substituted benzenes with olefins appears to occur from the excited singlet of benzene. Although still somewhat uncertain, 1,2 and 1,4 adducts seem to be formed from the same reactive species. The stereospecificity of these cycloadditions suggests the intermediate is highly symmetric. Exiplex formation also explains the stereospecificity of these reactions. However, there is a need to understand the chemistry of the exiplex in terms of its stability as a function of the olefin and the alkyl substituents on the benzene ring. The most direct evidence for an exiplex will have to come from spectroscopic data.

BIBLIOGRAPHY

1. J. M. Blair and D. Bryce-Smith, Proc. Chem. Soc., 287 (1957).
2. H. J. F. Angus, J. M. Blair and D. Bryce-Smith, J. Chem. Soc., 2003 (1960).
3. K. E. Wilzbach and L. Kaplan, J. Amer. Chem. Soc., 87, 4004 (1965).
4. K. E. Wilzbach, A. L. Harkness, and L. Kaplan, ibid., 90 116 (1968).
5. K. E. Wilzbach and L. Kaplan, ibid., 90, 3291 (1968).
6. G. R. Brubaker, Sem. Abst., U. of Ill., 61 (1973).

7. K. E. Wilzbach and L. Kaplan, J. Amer. Chem. Soc., 88, 2066 (1966).
8. Ibid., 93, 2073 (1971).
9. D. Bryce-Smith, A. Gilbert and B. H. Orger, Chem. Commun., 512 (1966).
10. R. Srinivasan, Tetrahedron Lett., 4551 (1971).
11. H. Morrison and W. I. Ferree, Jr., Chem. Commun., 268 (1969).
12. W. I. Ferree, Jr., J. B. Grutzner and H. Morrison, J. Amer. Chem. Soc., 93, 5502 (1971).
13. R. Hoffman and R. B. Woodward, Acc. Chem. Res., 1, 17 (1968).
14. D. Bryce-Smith and H. C. Longuet-Higgins, Chem. Commun., 593 (1968).
15. D. Bryce-Smith, A. Gilbert and H. C. Longuet-Higgins, ibid., 240 (1967).
16. D. Bryce-Smith, ibid., 806 (1969).
17. R. Srinivasan, J. Amer. Chem. Soc., 93, 3555 (1971).
18. H. J. F. Angus and D. Bryce-Smith, J. Chem. Soc., 4791 (1960).
19. G. O. Schenck and R. Steinmetz, Tetrahedron Lett., 21, 1 (1960).
20. J. G. Atkinson, D. E. Ayer, G. Buchi and E. W. Robb, J. Amer. Chem. Soc., 85, 2257 (1963).
21. R. Srinivasan and K. A. Hill, ibid., 78, 4653 (1965).
22. K. Koltzenburg and K. Kraft, Tetrahedron Lett., 389 (1966).
23. W. G. Dauben and G. J. Fonken, J. Amer. Chem. Soc., 81 4060)1959).
24. O. L. Chapman, G. W. Borden, R. W. King and B. Winkler, ibid., 86, 2660 (1964).
25. A. Morikawa, S. Brownstein and R. J. Cvetanovic, ibid., 92, 1471 (1970).
26. R. Srinivasan, ibid., 92, 7542 (1970).
27. A. Morikawa and R. J. Cvetanovic, J. Chem. Phys., 49, 1214 (1968).
28. H. Ishikawa and W. A. Noyes, Jr., ibid., 37, 583 (1962).
29. R. Srinivasan, J. Phys. Chem., 76, 15 (1972).
30. D. R. Arnold and V. Y. Arbaitys, Mol. Photochem., 2, 27 (1970).
31. N. Morrison and R. Peiffer, J. Amer. Chem. Soc., 90, 3428 (1968).
32. K. Kraft and K. Koltzenburg, Tetrahedron Lett., 4723 (1967); Pure Appl. Chem., 16, 125 (1968).
33. N. J. Turro, P. A. Wreide and J. C. Dalton, J. Amer. Chem. Soc., 90, 3274 (1968).
34. R. Srinivasan, ibid., 94, 8117 (1972).
35. J. Cornelisse, V. Y. Merritt and R. Srinivasan, ibid., 95, 6197 (1973).

ORGANIC SEMINAR ABSTRACTS

1974-75

Semester I

THE LIBRARY OF THE
MAR - 5 1975
UNIVERSITY OF ILLINOIS

School of Chemical Sciences
Department of Chemistry
University of Illinois
Urbana, Illinois

5+7

SEMINAR TOPICS

I Semester 1974-75

A Survey of Synthetic Methods to α-Methylene-γ-Butyrolactones......1
Richard Amos

3/7/75

The Organic Chemistry of π-Arene(π-Cyclopentadienyl)iron(II) Cations..10
Mark S. Pavlin

Sulfilimine Chemistry..18
Karl Wiegers

Stereochemical Elucidation Using Lanthanide NMR Shift Reagents ...28
David Sikkenga

Vinyloxyboranes as Synthetic Intermediates 30
Ikram M. Said

Azasulfonium Salts: Intermediates for Synthesis 32
William F. Pfohl

Synthetic Approaches to Epipolythiodiketopiperazines 34
Arthur Haber

Some Approaches to the Synthesis of Macrocyclic Compounds.........36
Marvin Reich

The Wiswesser Line-Formula Chemical Notation: A Novel Approach to Searching Chemical Literature 45
WILLIAM TODSEN

Recent Developments in Propellane Chemistry 55
David B. Reitz

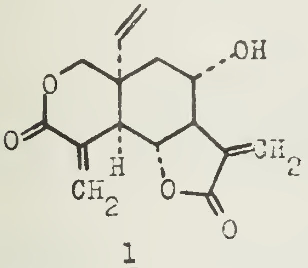
Crown Ethers: Control of Ion Structure and Reactivity 64
Maruice J. Baillargeon

A SURVEY OF SYNTHETIC METHODS TO α-METHYLENE-γ-BUTYROLACTONES

Reported by Richard Amos October 17, 1974

INTRODUCTION

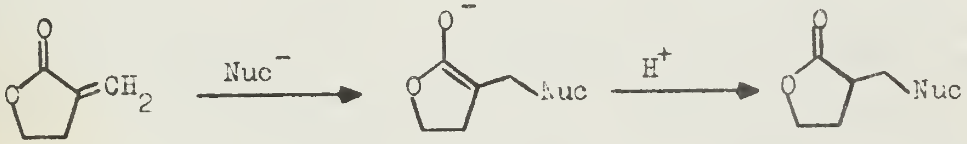
The occurrence of the α-methylene-γ-butyrolactone moiety in a wide variety of sesquiterpenes, now numbered at more than 400 and still increasing,[1] has generated a great deal of interest in the synthesis of this functionality. The compounds have taken on added importance due to their wide ranging biological activity, including cytotoxic and anti-tumor activity,[2] fungitoxicity,[3,4] and plant growth inhibition.[5] A classic example of this type of compound is vernolepin, 1.



1

To determine the role of the α-methylene-γ-butyrolactone portion of this molecule, a series of partial hydrogenations was carried out.[2] The dihydro compound, resulting from saturation of the angular vinyl group, was found to have nearly the same cytotoxicity as 1, whereas the tetrahydro compound, resulting from further reduction to the α-methyl-γ-butyrolactone ring, was found to be much less active. The results also suggest that the α-methylene-δ-valerolactones are much less effective in imparting cytotoxicity, and surprisingly, no monofunctional α-methylene-δ-valerolactones have been found to have significant activity.[2]

This biological activity appears to be the result of a rapid and essentially irreversible 1,4 addition of a nucleophile as shown.[6] In living systems the most likely nucleophiles appear to be cysteine residues, either as the free amino acid or in peptide chains.



Some human cancer cells have an absolute nutritional requirement for L-cysteine, apparently due to a defect in a biosynthetic pathway that allows normal cells to grow in the absence of L-cysteine. Thus, anti-tumor activity may be in part due to a cysteine scavenging role by the α-methylene-γ-butyrolactone functionality: the toxicity of such compounds is probably due to interference with the normal function of sulfhydryl groups on essential proteins.[7]

This presentation will deal with the scope of synthetic methods available for the α-methylene-γ-butyrolactone group with some coverage of the δ lactone also. The topical organization is based on starting materials used in the synthesis.

Two important goals are served by the preparation of synthetic lactones. First is the derivation of structure-activity relationships. Second, the naturally occurring lactones are quite toxic, due in part to the multiple functionalities present. Convenient syntheses of simpler compounds might lead to an effective but less toxic drug.[7]

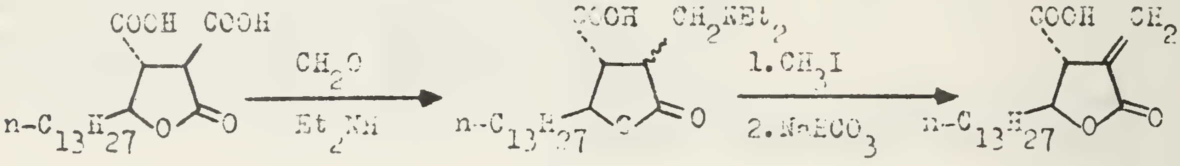
I. FROM ACETYLENIC CARBINOLS

The parent compound, α-methylene-γ-butyrolactone, was first isolated by Cavallito after hydrolysis of a presumed glycosidic precursor from Erythronium americanum, and was shown to have antibacterial activity.[8] The first reported synthesis was by Jones and co-workers in 1950,[9] treating but-3-yn-1-ol with nickel carbonyl in an aqueous ethanol-acetic acid solvent to give 23% of the desired product. The secondary and tertiary alcohols gave 30% and 10% of γ-methyl- and γ, γ-dimethyl-α-methylene-γ-butyrolactones, respectively. A γ, δ-acetylenic carbinol gave 20% of the α-methylene-δ-valerolactone.

II. FROM EXISTING LACTONE STRUCTURES

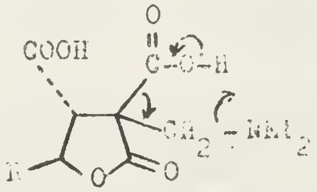
A. Mannich reaction

One of the earliest and still frequently used[7] methods involves the formation of a Mannich base at an active hydrogen site on the lactone ring, followed by a β-elimination to give the methylene group. van Tamelen and Bach first applied the procedure to give α-methylene-γ-phenyl-γ-butyrolactone from α-carboxy-γ-phenyl-γ-butyrolactone[10] (later shown to have been the β-phenyl isomer instead[12]). The synthesis of dl-protolichesterinic acid, 4, proceeded by Mannich base formation, quaternization, and elimination to give the product in 37% yield.[11]

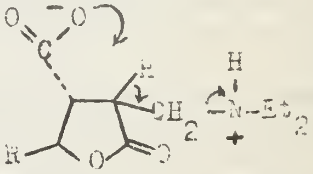


2 3 4

The precursor, 2, was prepared by reaction of the dimethylmalonate anion with methyl 3-tridecylglycidate. During the synthesis of 3, the authors also isolated a substantial amount of 4 formed directly from 2, attributing this to either a concerted decarboxylation-elimination of the initially formed α-carboxy-α-N,N-diethylaminomethyllactone, 5, or to a self-induced β-elimination, 6, following an α-decarboxylation.



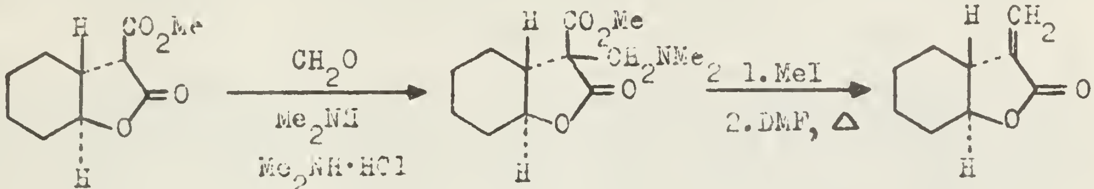
5



6

Dalton and Elmes[12] propose that the sole reaction pathway is the concerted decarboxylation-elimination route and that the formation of 3 can be attributed to a Michael addition of the liberated amine to the α-methylene lactone. They found the γ-phenyl- and β-phenyl-α-carboxy-γ-butyrolactones gave the respective α-methylene lactones in good yield directly by heating with diethylamine and formalin for 15 minutes, followed by immediate extraction. Nmr studies showed a rapid appearance of the exocyclic methylene protons, followed by their gradual disappearance with extended reaction times as the Michael adduct formed. There are reports that treatment of the initial product with NaOAc-HOAc is required to effect conversion[16,20], but this appears to be highly dependent upon the lactone.[12,17] Miller and Smith have applied the Mannich reaction to the regioselective formation of α-methylene ketones.[21]

Behare and Miller[13] have noted that esterification of the carboxyl group allows isolation of the initially formed Mannich base. Quaternization and thermal decarboxylation-elimination gives the desired product, 7, in 67% yield.



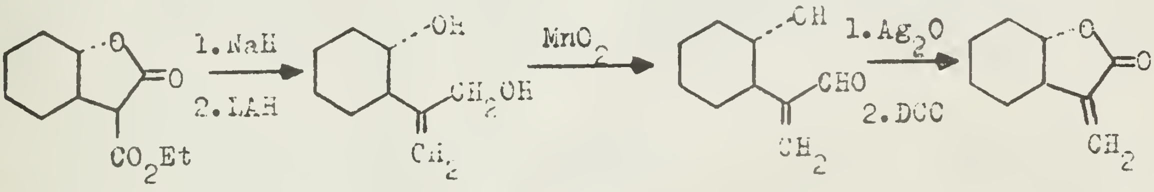
7

This procedure appears not to be universal since Dalton[14] reports that fluorene-9-spiro-3'-(2'-ethoxycarbonylbutyrolactone) would not form a Mannich base under these conditions.

The α-carboxy lactones needed for the preceeding methods can be prepared readily from the lactones themselves. Grieco[15] found that both γ and δ lactone enolates, generated with LDA (lithium diisopropylamide), react in high yield with CO_2 gas. Stiles reagent, methyl methoxymagnesium carbonate, has been used to effect carboxylation, although the procedure is limited to γ-lactones. The reagent has been used in the synthesis of three natural products: dl-protolichesterinic acid,[17] dl-4-isoavenaciolide,[18] and dl-avenaciolide.[19,20]

B. Reduction of lactone enolates

Marshall and Cohen[22,23] reduced the sodioenolate of 8 with LAH to give the diol, 9, in a 40% yield. Selective oxidation to the hydroxyaldehyde, 10, with MnO_2 occurred in 85% yield, followed by Ag_2O oxidation (93.5%) and a DCC cyclization (59%).

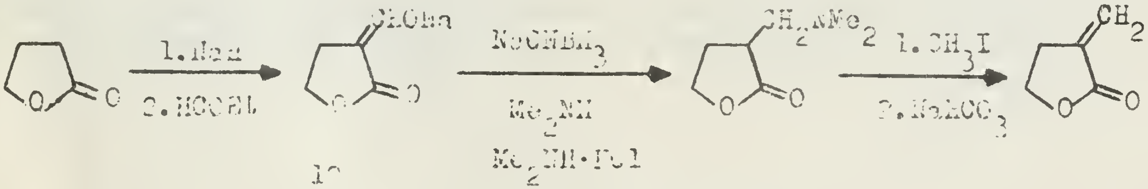


8 9 10 11

The authors report that the cis isomer undergoes MnO_2 oxidation to give a 60% yield of cis fused 11 directly. Apparently the cis geometry of the hydroxyaldehyde allows cyclization to the lactol, which is then oxidized to the lactone. Both the cis and trans lactones fused to the more flexible cycloheptane ring can be directly cyclized. This method has been used to prepare a variety of natural products.[24-28] Golfier and Prangé[29] have used Ag_2CO_3 to effect oxidation of an acyclic diol, akin to 9 without the cyclohexane ring, to give the α-methylene lactone directly in an 80% yield.

C. Reductive amination of α-formyl lactones

Hutchinson has recently reported[3,30] the reductive amination of the sodium salt of α-hydroxymethylene-γ-butyrolactone, 12, using dimethylamine-dimethylamine hydrochloride and sodium cyanoborohydride. Yield overall was



12

70% and the δ lactone system was found to give a 20% yield. In a similar manner Yamada[31] catalytically hydrogenated the enamine derived from an α-formyl lactone and diethylamine and then heated with NaOAc-HOAc to give the α-methylene-γ-butyrolactone in a 60% yield. A δ lactone gave a 42% yield.

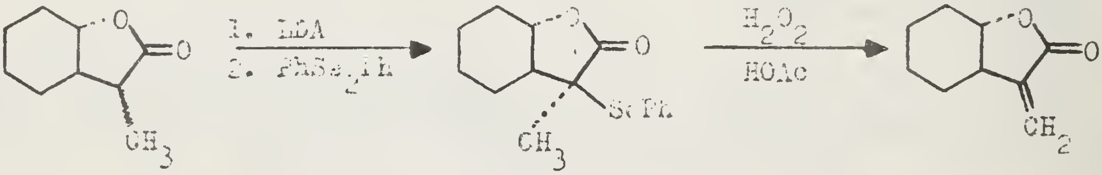
D. Dehydration of α-hydroxymethyl lactones

A variety of synthetic methods exist for the introduction of the α-hydroxymethyl group into the lactone ring. For example, the α-formyl group, introduced via NaH and HCO_2Et, can be reduced either by catalytic hydrogenation[32-36] or by $NaBH_4$ reduction.[32,33] Greico has carried out direct α-hydroxymethylations by reacting the lactone enolate with gaseous formaldehyde, making the conversions of both γ and δ lactones in > 95% yield.[37] This method has been applied in model studies toward the total synthesis of vernolepin, 1.[38,39] Finally, Yamada and co-workers[31] have treated an α-carboxy lactone with N,N'-carbonyldiimidazole followed by reduction with $Zn(BH_4)_2$ to give the α-hydroxymethyl lactone in a 45% yield.

The dehydration of the α-hydroxymethyl lactone has been accomplished by passage over an alumina catalyst heated to 340-350°C,[36] by elimination of the tosylate or mesylate derivative in refluxing pyridine,[32-35, 37-39] and by the action of triphenyl phosphite methiodide[31] or dicyclohexylcarbodiimide.[40]

E. Via α-phenylseleno and α-phenylsulfinyl lactones

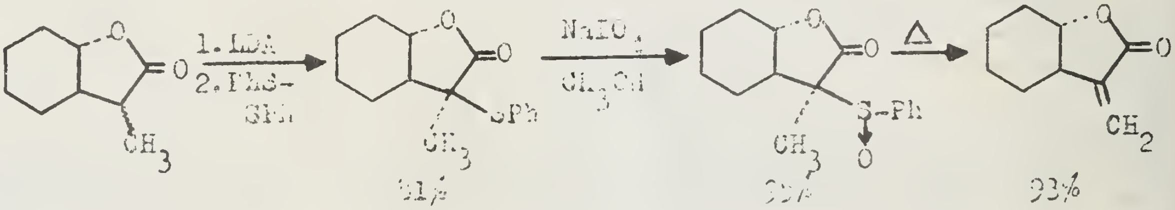
Grieco[41] has developed a general procedure for the conversion of cis and trans fused γ- and δ-lactones into their respective α-methylene compounds via a syn elimination of alkylphenyl selenoxides. Methylation of the trans fused lactone with LDA and CH_3I gave 13 in a > 95% yield. Regeneration of the lactone enolate with LDA and treatment with diphenyl diselenide gave 85% of 14, which was oxidized with 30% H_2O_2 to give 15 in 96% yield.



13 14 15

The exclusive formation of the 14 epimer plus the syn elimination gave only 15, with no evidence of the endocyclic isomer. The conversion of cis fused lactones requires that the methylation and selenenylation steps be reversed so as to maintain the anti geometry between the selenoxide group and the methine proton to prevent endocyclic elimination.

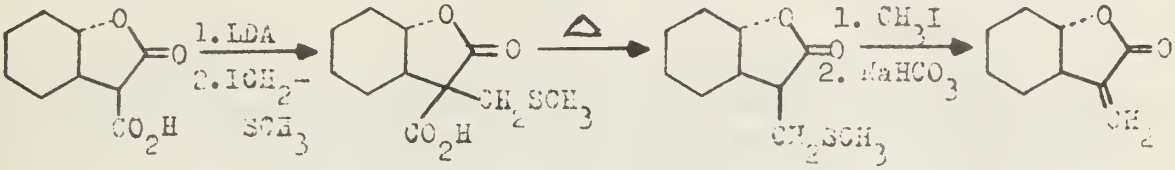
A second very similar approach by Grieco[42] utilizes the thermal elimination of sulfoxides to generate the α-methylene moiety.



Again, application to the cis fused lactone required that the methylation and phenylsulfenylation steps be reversed. Reich and Renga[43] have used a similar thermal elimination of sulfoxides to make α-methylene ketones and carboxylic acids.

F. Via thioethers

Ronald[44] has used β-elimination of thioethers to generate the α-methylene function, isolable in the protected form 16 if desired. The same reaction sequence was applied to cis and trans fused lactones.



>95%   16   86%   95%

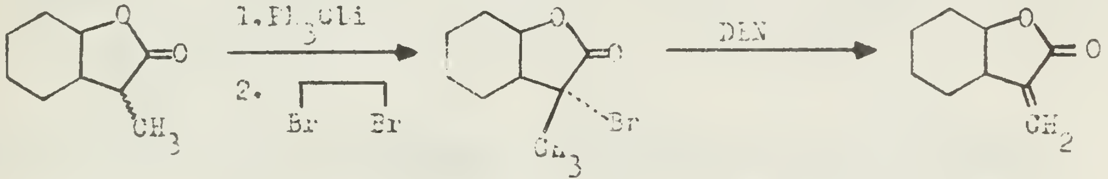
G. Via the Wittig reaction

Grieco[45] has found that γ-butyrolactonylidene triphenylphosphorane reacts with paraformaldehyde in nearly quantitative yield to give α-methylene-γ-butyrolactone. Howie and co-workers[6] have extended the scope of the reaction by using a variety of dialdehydes to give difunctional molecules having two substituted α-methylene groups. Only the E isomers were produced when benzene was used as the solvent, but DMSO and toluene gave small amounts of the Z isomers. When tested for activity, these compounds were found to have low cytotoxicities despite their difunctional character, indicating that alkyl substitution of the α-methylene group has a substantial deactivating effect.

III. FROM α-METHYL LACTONES

The availability of α-methyl lactones from either natural or synthetic sources make the α-methyl → α-methylene conversion attractive. Ourisson and co-workers[1,46,47] have developed methods paralleling those of Grieco,[41,42] wherein a leaving group is introduced α to the lactone carbonyl and then is eliminated to give the exocyclic product. The procedures do have an advantage in that the methyl precursor can be used with both cis and trans fused rings whereas Grieco's methods for cis compounds require the unsubstituted lactone as the precursor.

The anion of the cis fused lactone, 17, is generated by treatment with triphenylmethyllithium followed by bromination with 1,2-dibromoethane, giving exclusively the indicated isomer, 18. Dehydrohalogenation in 65% yield is accomplished with 1,5-diazabicyclononene, yielding only the exocyclic compound.



17   18

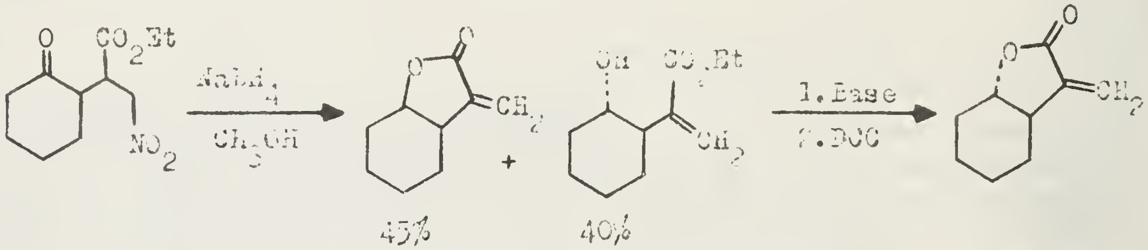
Since an anti elimination in the trans fused system would lead to the endocyclic product, a second procedure using the pyrolysis of an ester, known to be a syn elimination,[48] was developed. Treatment of the lactone enolate with dibenzoyl peroxide gave the α-benzoyloxylactone in a 50% yield (presumed to be a mixture of epimers). Pyrolysis at 600°C gave a 3:1 mixture of exocyclic:endocyclic in a 60% yield. When applied to the synthesis of a naturally occurring trans fused compound, (+)-arbusculin, the procedure gave only one ester isomer, and pyrolysis yielded only the desired exocyclic product.

IV. FROM α-CARBOXYMETHYL LACTONES

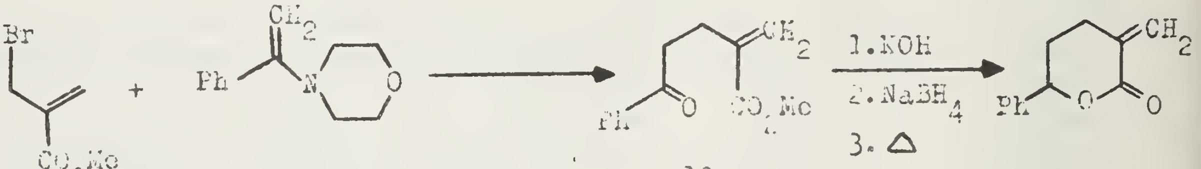
Two almost simultaneous reports have appeared[49,50] which describe formation of both α-methylene-γ- and -δ-lactones by oxidative decarboxylation of α-carboxymethyl lactones using lead tetraacetate in the presence of cupric acetate.

V. FROM KETONES

Patterson and McMurry[51] have found that ketones can be converted to fused ring α-methylene lactones via enamine formation, Michael addition to ethyl β-nitroacrylate, and borohydride reduction with lactonization and elimination of the nitro group occurring during a 10 hour reflux.

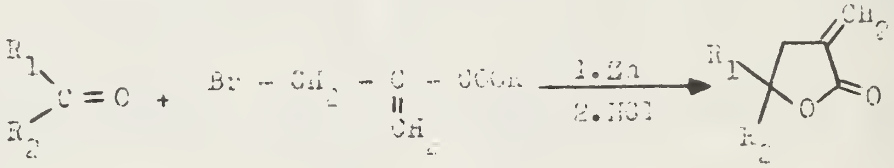


Access to δ lactones is provided by the reaction of methyl α-bromomethylacrylate with the morpholine enamine of acetophenone to give 19 in a 50% yield.[52] Saponification, reduction, and lactonization gave the desired product in 75% yield. A number of ketones gave similar results with varying yields.



19

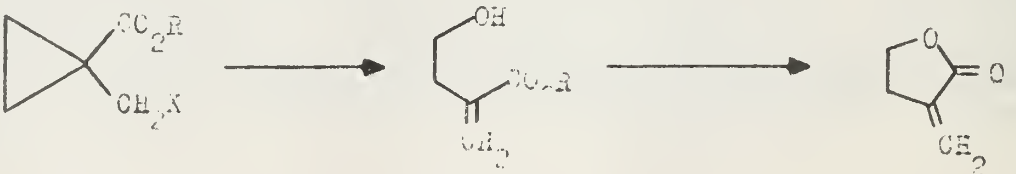
Öhler and co-workers[53] have reacted a variety of aldehydes and ketones with α-(bromomethyl)-acrylic esters in the presence of zinc metal in a Reformatsky type reaction to give α-methylene-γ-butyrolactones.



Yields range from 42 - 100% with aromatic R groups showing the highest yields. Rosowsky[7] and Löffler[54] have also applied this method.

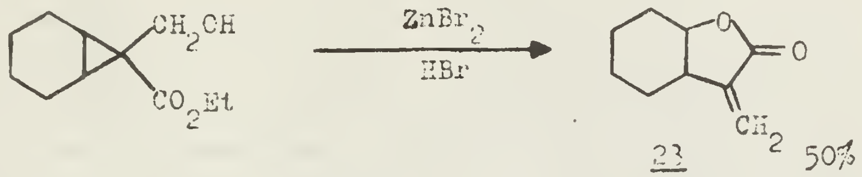
VI. FROM CYCLOPROPANES

The homoallylic alcohol, 21, can be considered as a precursor for the desired α-methylene-γ-butyrolactone, 22, and is derivable from a suitable cyclopropylcarbinyl compound, 20.



20 21 22

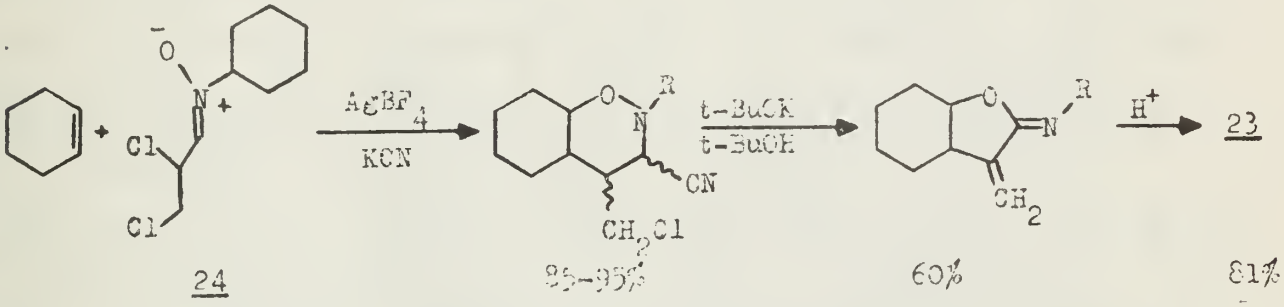
Hudrlik and co-workers[55], using this thesis, found that ethyl 1-hydroxymethylcyclopropanecarboxylate reacted with excess $ZnBr_2$ in 48% HBr to give 22 in a 25% yield. To study the stereochemistry, the equivalent reaction in a fused ring system was studied. It appears that the secondary homoallylic cation,



formed by the ring opening reacts intramolecularly with the ester group to give only the product with the cis configuration. The trans isomer of 23 was shown to be stable under the reaction conditions, and thus can not be an intermediate.

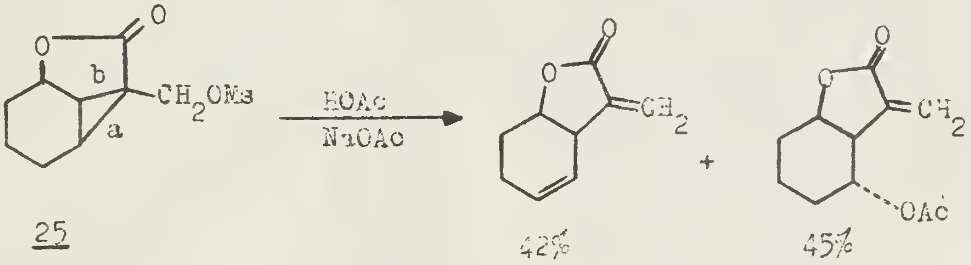
VII. FROM ALKENES

α-Chloro-aldonitrones have been found to react with alkenes to give Ag^+ induced (4 + 2) cycloaddition products which can be readily converted to lactones.[56] In a recent report[57] the cyclohexylnitrone 24, formed from 2,3-dichloropropanal, was reacted with both cyclohexene and 1,2-dimethylcyclohexene to form, after elimination and hydrolysis, the respective α-methylene-γ-butyrolactones.



VIII. MISC. METHODS

Ziegler[58] has developed a method of producing α-methylene lactones possessing a homoallylic ester group, a structural feature which appears to enhance the cytotoxicity of the compounds.[2] Treatment of 25 with refluxing HOAc containing 1.2 equivalents of NaOAc gave two major products. Bond a is



the site of solvolysis because it can receive stabilization in the transition state by π overlap with the lactone carbonyl whereas bond b is orthogonal to the π bond.

In one of the earliest syntheses of α-methylene-γ-butyrolactones, Piskov[59] treated 2,3,3-tricarbethoxy-1-propene with paraformaldehyde and a catalytic amount of KOH to give β-carboxy-α-methylene-γ-butyrolactone.

IX. PROTECTING GROUPS

In the synthesis of complex molecules containing the α-methylene lactone moiety, it occasionally may be advantageous to introduce the function at an early stage. Later synthetic conversions may require the use of a protecting group due to the high reactivity of the function. A Michael addition of dimethylamine to the α-methylene group gives a stable adduct which can then be converted back by use of methyl iodide and pyrolysis of the salt.[60,61] Kupchan[62] has used 1-propanethiol to form the adduct followed by treatment with CH_3I and $NaHCO_3$ to effect the regeneration of the α-methylene lactone. He feels this method is better than the amine adduct since regeneration conditions are milder and the mercaptide anion is more nuclephilic. Grieco[63] has used a Michael addition of the phenyl selenium anion to the α-methylene group to generate a stable adduct. Treatment with 30% H_2O_2 in THF regenerates the product in high yield. It should be pointed out that a number of syntheses previously described initially provide the α-methylene function in a protected form and this could be used to avoid additional protecting reactions.

CONCLUSION

While a wide variety of synthetic methods do exist for the preparation of α-methylene lactones, the majority of studies have involved model systems. The real test will come in their synthesis of more complex natural products and synthetic drugs.

BIBLIOGRAPHY

1. A. E. Greene, J-C. Muller, and G. Ourisson, J. Org. Chem., 39, 186 (1974).
2. S. M. Kupchan, M. A. Eakin, and A. M. Thomas, J. Med. Chem., 14, 1147 (1971).
3. C. R. Hutchinson, J. Org. Chem., 39, 1854 (1974).
4. B. H. H. Bergman, J. C. M. Beijersbergen, J. C. Overeem, and A. Kaars Sijpesteijn, Rec. Trav. Chim., 86, 709 (1967).
5. Y. Iino, A. Tanaka, and K. Yamashita, Agr. Biol. Chem., 36, 2505 (1972).
6. G. A. Howie, P. E. Manni, and J. M. Cassady, J. Med. Chem., 17, 840 (1974).
7. A. Rosowsky, N. Papathanasopoulos, H. Lazarus, G. E. Foley, and E. J. Modest, ibid., 17, 672 (1974).
8. C. J. Cavallito and T. H. Haskell, J. Am. Chem. Soc., 68, 2332 (1946).
9. E. R. H. Jones, T. Y. Shen, and M. C. Whiting, J. Chem. Soc., 230 (1950).
10. E. E. van Tamelen and S. R. Bach, J. Am. Chem. Soc., 77, 4683 (1955).
11. E. E. van Tamelen and S. R. Bach, ibid., 80, 3079 (1958).
12. L. K. Dalton and B. C. Elmes, Aust. J. Chem., 25, 625 (1972).
13. E. S. Behare and R. B. Miller, Chem. Comm., 402 (1970).
14. L. K. Dalton, B. C. Elmes, and B. V. Kolczynski, Aust. J. Chem., 25, 633 (1972).
15. P. A. Grieco and K. Hiroi, Chem. Comm., 500 (1973).
16. J. Martin, P. C. Watts, and F. Johnson, ibid., 27 (1970).
17. J. Martin, P. C. Watts, and F. Johnson, J. Org. Chem., 39, 1676 (1974).
18. K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, Chem. Comm., 499 (1973).
19. W. L. Parker, and F. Johnson, J. Am. Chem. Soc., 91, 7208 (1969).
20. W. L. Parker, and F. Johnson, J. Org. Chem., 38, 2489 (1973).
21. R. B. Miller and B. F. Smith, Tetrahedron Lett., 5037 (1973).
22. J. A. Marshall and N. Cohen, J. Org. Chem., 30, 3475 (1965).
23. J. A. Marshall and N. Cohen, Tetrahedron Lett., 1997 (1964).
24. J. A. Marshall, N. Cohen, and K. R. Arenson, J. Org. Chem., 30, 762 (1965).
25. J. A. Marshall and N. Cohen, J. Am. Chem. Soc., 87, 2773 (1965).
26. J. A. Marshall, N. Cohen, and A. R. Hochstetler, ibid., 88, 3408 (1966).
27. J. A. Marshall and A. R. Hochstetler, Tetrahedron Lett., 55 (1966).
28. V. R. Tadwalkar and A. S. Rao, Indian J. Chem., 9, 1416 (1971).
29. M. Golfier and T. Prangé, Bull. Soc. Chim. Fr., 1158 (1974).
30. A. D. Harmon and C. R. Hutchinson, Tetrahedron Lett., 1293 (1973).
31. K. Yamada, M. Kato, and Y. Hirata, Tetrahedron Lett. 2745 (1973).
32. H. Minato and I. Horibe, Chem. Comm., 531 (1965).
33. H. Minato and I. Horibe, J. Chem. Soc. (C), 1575 (1967).
34. H. Minato and I. Horibe, ibid., 2131 (1968).

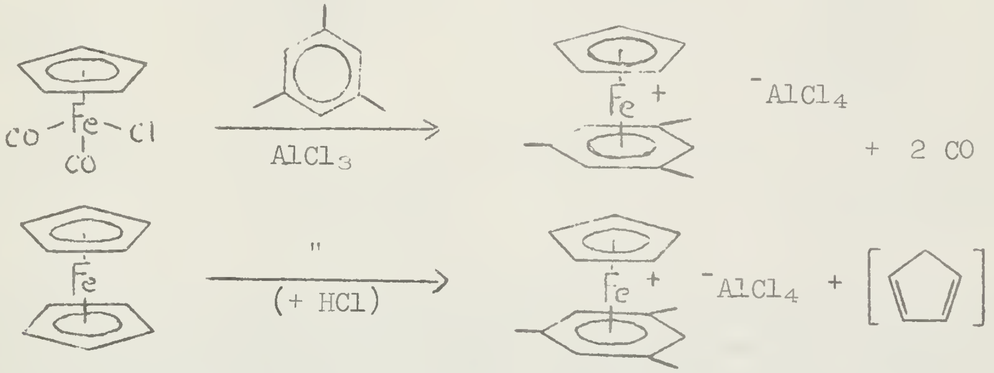
35. H. Minato and I. Horibe, Chem. Comm., 358 (1967).
36. Wm. J. McGraw, U.S. Patent 2,624,723, Chem. Abstr., 47, 11232h (1953).
37. P. A. Grieco and K. Hiroi, Chem. Comm., 1317 (1972).
38. P. A. Grieco and K. Hiroi, Tetrahedron Lett. 1831 (1973).
39. R. D. Clark and C. H. Heathcock, ibid., 1713 (1974).
40. C. Alexandre and F. Rouessac, C. R. Acad. Sci. Ser. C, 274, 1585 (1972).
41. P. A. Grieco and M. Miyashita, J. Org. Chem., 39, 120 (1974).
42. P. A. Grieco and J. J. Reap, Tetrahedron Lett., 1097 (1974).
43. H. J. Reich and J. M. Renga, Chem. Comm., 135 (1974).
44. R. C. Ronald, Tetrahedron Lett., 3831 (1973).
45. P. A. Grieco and C. S. Pogonowski, J. Org. Chem., 39, 1958 (1974).
46. A. E. Greene, J-C. Muller, and G. Ourisson, Tetrahedron Lett. 2489 (1972).
47. A. E. Greene, J-C. Muller, and G. Ourisson, ibid., 3375 (1972).
48. C. H. DePuy and R. W. King, Chem. Rev., 60, 431 (1960).
49. K. J. Divakar, P. P. Sane, and A. S. Rao, Tetrahedron Lett., 399 (1974).
50. T. Ho and C. M. Wong, Syn. Comm., 4, 133 (1974).
51. J. W. Patterson and J. E. McMurry, Chem. Comm., 488 (1971).
52. A. Tanaka, T. Nakata, and K. Yamashita, Agr. Biol. Chem., 37, 2365 (1973).
53. E. Ohler, K. Reininger, and U. Schmidt, Angew. Chem. Int. Ed. Engl., 9, 457 (1970).
54. A. Löffler, R. D. Pratt, J. Pucknat, G. Gelbard, and A. S. Dreiding, Chimia, 23, 413 (1969).
55. P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, J. Am. Chem. Soc., 95, 6848 (1973).
56. T. K. Das Gupta, D. Felix, U. M. Kempe, and A. Eschenmoser, Helv. Chim. Acta, 55, 2198 (1972).
57. M. Petrzilka, D. Felix, and A. Eschenmoser, ibid., 56, 2950 (1973).
58. F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Studt, Tetrahedron Lett., 2035 (1974).
59. V. B. Piskov, J. Gen. Chem., USSR, 30, 1421 (1960).
60. N. R. Unde, S. V. Hiremath, G. H. Kulkarni, and G. R. Kelkar, Tetrahedron Lett., 4861 (1968).
61. T. C. Jain, C. M. Banks, and J. E. McCloskey, ibid., 841 (1970).
62. S. M. Kupchan, T. J. Giacobbe, and I. S. Krull, ibid., 2859 (1970).
63. P. A. Grieco and M. Miyashita, ibid., 1869 (1974).

THE ORGANIC CHEMISTRY OF π-ARENE(π-CYCLOPENTADIENYL)IRON(II) CATIONS

Reported by Mark S. Pavlin October 24, 1974

Organometallic chemists have long been interested in bis-cyclopentadienyl(cpd) and bis-benzenoid metal "sandwich" complexes such as ferrocene and dibenzenechromium. Research has also been focused on "mixed sandwich" systems in which two different aromatic ring ligands are π-bonded to the same central metal atom. The first such compounds, reported in 1957[1], were benzene(π-methylcpd)manganese(I) and mesitylene(π-cpd)iron(II) iodide prepared from 1,1'-dimethylmanganocene with phenylmagnesium bromide and (cpd)iron dicarbonyl chloride with mesitylene, respectively. In 1963 a number of these "mixed sandwich" complexes of iron were synthesized directly from ferrocene via a similar ligand exchange reaction.[2] In a formal sense, the latter exchange process is viewed as the replacement of a six-electron, negatively charged ligand with a six-electron, neutral ligand (Scheme I). The central iron atom in this "mixed sandwich" complex bears a positive charge although its oxidation state remains unchanged.

Scheme I



This review deals with the scope of the ligand exchange reaction of ferrocene as well as with the chemistry of the arene(π-cpd)iron(II) cation products. Sections of two review articles have partially surveyed the topic.[3,4]

PREPARATION AND PROPERTIES OF π-ARENE(π-cpd)IRON(II) CATIONS

Nesmayanov, et al. obtained benzene(π-cpd)iron(II) tetraphenylborate(1a) in 61% yield(based on ferrocene consumed) by refluxing ferrocene, aluminum dust and aluminum chloride(molar ratio 1:1:2) in benzene under nitrogen and treating the hydrolyzate with $NaBPh_4$. Oxidation of ferrocene became a serious side reaction when the aluminum dust was excluded(ferricinium ion did not undergo ligand exchange). Alkylated[2] and halogenated benzenes[5,6] gave modest yields of substituted arene(π-cpd)iron(II) cations. Dehalogenation occurred during the reaction of bromobenzene giving a mixture of π-benzene and π-bromobenzene compounds. Side reactions were so serious in the case of iodobenzene that none of the desired arene(π-cpd)iron complex was formed.

In general, ligand exchange reactions were carried out with the arene itself or a high-boiling hydrocarbon as solvent. Cation products were extracted into water and precipitated from aqueous solution with BF_4^-, BPh_4^-, PF_6^- or Reineckate anions giving yellow, air stable but somewhat light-sensitive, powdered or crystalline salts. Most of these salts decomposed upon heating or melting and yielded ferrocene upon pyrolysis. Triiodide, iodide, and tribromide salts, although less stable, have also been prepared. The results of a representative number of ligand exchange reactions with ferrocene are summarized in Table I.

Table I. Reaction Data for $AlCl_3$-Catalyzed Ligand Exchange With Ferrocene and Various Benzenoid Compounds to Give [π-Arene(π-cpd)iron(II)]$^+$ X^- (1a-j).

	Arene	X^-	Reaction Time (hr)	Reaction Temperature(°C)	Yield(%)	Decompositio Temperature(
1a.	benzene	BPh_4	6.0	80	20	250-251
1b.	toluene	BPh_4	5.0	110	37	246-246.5
1c.	mesitylene	BPh_4	3.0	160	22	257-258
1d.	tetralin	BPh_4	3.5	160-165	16	237.5-238.5
1e.	biphenyl	BF_4	3.0	160-170	40	134-135[a]
1f.	naphthalene	BF_4	3.5	110-120	33	131.5-133[a]
1g.	fluorene	BPh_4	3.5	135-140	25	218-219
1h.	chlorobenzene	BF_4	3.0	130-135	25	214
1i.	acetanilide	PF_6	5.0	115-125	23	160.5-162[a]
1j.	diphenyl ether	PF_6	3.5	125	-	131.5-132.5

[a] Melting point

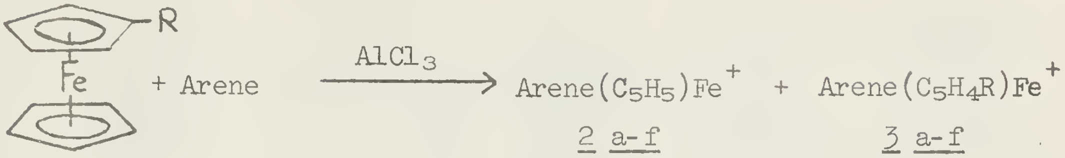
Both the ^{1}H-nmr[4,7,8,9] and ^{13}C-nmr[10,11] spectra of the cations exhibit arene signals at higher fields than the signals seen for the uncomplexed arene. For example, the benzene ^{1}H-nmr resonance of 1a appears at δ 6.50 compared to 7.27 for benzene itself; the benzene ^{13}C-nmr resonance of 1a appears at δ_c 88.5, well above that of benzene(128.5) and benzenechromium tricarbonyl (92.4). This dramatic upfield shift is credited to both the proximity of the positive charge on iron and the reduction of ring anisotropy due to ring electron density donation to iron. The chemical shifts of a variety of cations correlated well with the Hammett-Taft parameters σ_p^o, σ_i, and σ_r^o.[8]

Nesmayanov observed that ligand exchange was facilitated by electron donating substituents on either the arene or cpd ring; electron withdrawing substituents retarded exchange. Thus, mesitylene exchanged[12] with a cpd ring of 1,1'-diethylferrocene at 90-100° in 32% yield, with one of ferrocene in 20% yield and one of 1,1'-diacetylferrocene in only 4% yield. 1,1'-Dicyanoferrocene did not react with benzene at all. Furthermore, acetophenone and benzonitrile failed to give any ligand exchange with ferrocene. Astruc and Dabard[9] later confirmed these observations but noted that alkyl substituents larger than ethyl on ferrocene depressed reaction yields because of their steric bulk.

Another manifestation of these electronic effects is seen when benzene or mesitylene are reacted with mono-substituted ferrocenes[9,12]: the more electron rich cpd ring exchanges preferentially. This is illustrated in Table II.

Little is known about the mechanistic details of the ligand exchange process. Bublitz suggests that ligand exchange takes place through the same intermediates as the scrambling of cpd rings when ferrocene react with

Table II. Competition for the Exchange of the Substituted or Unsubstituted cpd Ring Ligand in Mono-Substituted Ferrocenes.

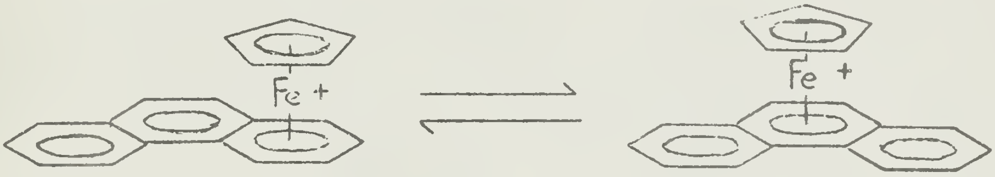


	R	Arene	Yield(%) 2 + 3	Molar Ratio 2 : 3
a.	CH_3	benzene	-	2.1 : 1
b.	C_2H_5	"	30	2.7 : 1
	"	mesitylene	30	7.8 : 1
c.	n-C_3H_7	benzene	18	3.3 : 1
d.	CH_2Ph	"	22	2.0 : 1
e.	$COCH_3$	"	25	1 : 1.04
	"	mesitylene	-	1 : 3.8
f.	CN	benzene	-	1 : 4.3

aluminum and gallium trihalides.[13] Slocum and Ernst speculate[4] that the species $[Fe(\pi\text{-}cpd)]^+$, formed by the $AlCl_3$ promoted cleavage of one of the ferrocene ring-metal bonds, is quenched by the aromatic solvent(or co-solvent) to give the observed "mixed sandwich" products.

LIGAND EXCHANGE WITH POLYNUCLEAR AROMATIC MOLECULES

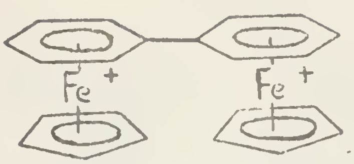
With the arene in excess, ferrocene ligand exchange with biphenyl, naphthalene, fluorene and phenanthrene gave the expected cations 1e-g, and 4. The exact structure of 4 (4a, 4b, a mixture of 4a and 4b or the fluxional compound 4a⇌4b) has not been determined.



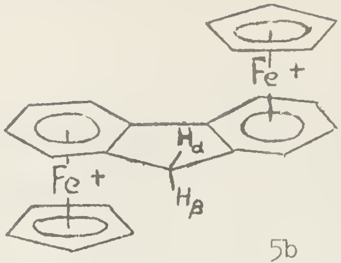
4a

4b

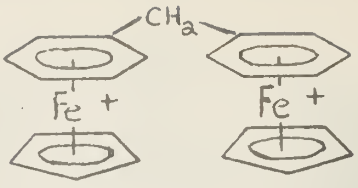
Sutherland, Thomson and Lee[14] synthesized the first π-arene-bis((π-cpd) iron(II))dications 5a-c by reacting the corresponding mono-cations with excess ferrocene under the usual conditions. They demonstrated the transoid nature of 5b from its ^1H-nmr spectrum; whereas the fluorene(π-cpd)iron(II) cation showed a doublet of doublets for protons Hα and Hβ, the dication showed a singlet. Recently dications 5a-c have been prepared directly from ferrocene (in excess) and the polynuclear aromatic molecule.[11] Anthracene, p-terphenyl and chrysene were among other polyaromatics that also gave dications.



5a



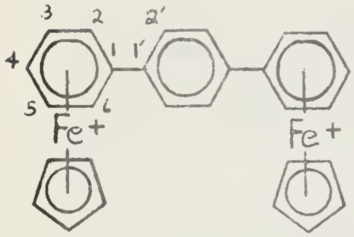
5b



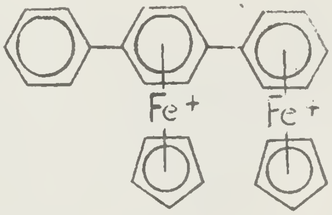
5c

Again, the ^{13}C-nmr spectra of these dications are of special interest. Carbon atoms in aromatic rings substituted by the Fe(cpd) moiety showed the same strong upfield shift observed in the simpler benzenoid cases (i.e. a shift from the normal aromatic region of δ_c 130 to 85). However, the carbons of aromatic rings not substituted with Fe(cpd), even those fused to rings with the Fe(cpd) group attached, exhibited little upfield shift. Quaternary carbons at fused-ring junctions(such as the 9,10 carbons of naphthalene and the 11-14 carbons of anthracene) appear at an intermediate position(ca. δ_c 100) when one ring to which they belong is Fe(cpd) substituted and the other is not.

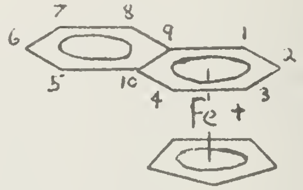
Thus structure 6a and not 6b was assigned to p-terphenyl-bis((π-cpd)iron (II)) dication. Its ^{13}C-nmr spectrum showed only one low-field peak (δ_c 136) and one high-field peak (δ_c 102) for the four quaternary carbon atoms 1 and 1' respectively. The corresponding spectrum of 6b would exhibit four separate lines for the same carbon atoms.



6a



6b



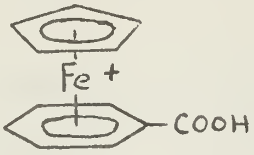
7

Naphthalene gave only the monocation(7) under a variety of experimental conditions. Six nonsolvent peaks were discernable in the ^{13}C-nmr of this compound; one for the cpd ring (δ 77.3), the 1(4) and 2(3) carbons(87.7, 86.1), the 9(10) quaternary carbons(96.9) and the 5(8) and 6(7) carbons on the unsubstituted ring(133.1, 131.8). These chemical shifts, it should be noted, argue against fluxional character in 7.

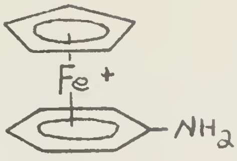
Attempts to trisubstitute a polynuclear aromatic compound failed in the cases of triphenylmethane and triphenylene. Polystyrene, however, gave a poly-(styrene(π-cpd)iron(II)cation) material with, on the average, one Fe(cpd) moiety attached to every third aromatic ring.[15] Tetraphenylporphine also gave a complex with more than two Fe(cpd)groups substituted.[16]

REACTIONS OF π-ARENE(π-cpd)IRON(II) CATIONS

In contrast to ferrocene with which it is isoelectronic, 1a is resistant to oxidation. It was recovered unchanged after treatment with either peroxide or chromic acid.[17] Exhaustive oxidation of 1c with aqueous permanganate gave uncomplexed trimesic acid in 57% yield. Oxidation of 1b with permanganate allowed isolation benzoic acid(π-cpd)iron(II)cation(8). Due to the electron density demands of the ring-metal bond and the proximity of the iron positive charge, 8 is a strong acid[18] (pK_a = 3.05 versus 5.65 for uncomplexed benzoic acid). Conversely, amine 9 prepared as described below, is a weaker base than aniline.[19]



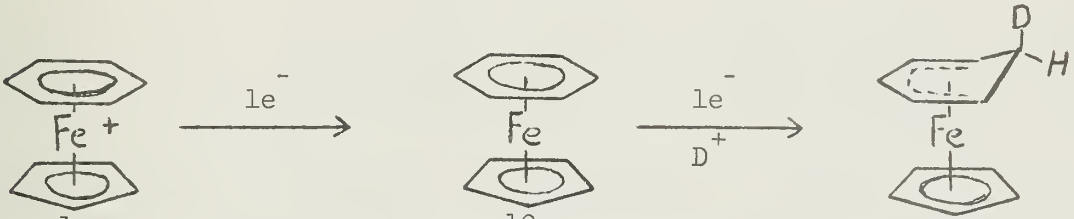
8



9

Reduction of the π-arene(π-cpd)iron(II) cations should lead to neutral iron(I) complexes. Formally 19-electron systems, these complexes would be unstable relative to the parent cation. Nesmayanov found this to be true when he reacted 1a with Na-Hg amalgam in THF.[20] The product, 10, could be stored only at -78° under dry argon. Heating to 40° decomposed 10 to benzene, ferrocene and iron salts. In the presence of naphthalene, CO and (PhO)$_3$P, 10 decomposed with ligand exchange giving 7(6%), cyclopentadienyliron(II) tricarbonyl dimer(70%) and cyclopentadienyliron(II) bis(triphenylphosphite) dimer(27%) respectively. This type of ligand exchange occured directly when 7 reacted with Na-Hg/THF in the presence of benzene or CO.[21]

Scheme II

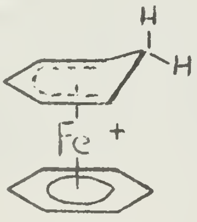


1a
one negative ligand
one neutral ligand
Fe(II)

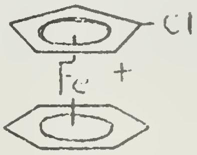
10
one negative ligand
one neutral ligand
Fe(I)

11
two negative
ligands
Fe(II)

Reductions using LiAlH$_4$ or NaBH$_4$ result in hydride addition to the arene ligand exclusively.[22] Studies on substituted arene cations[6,7] demonstrate that addition proceeds to an unsubstituted ring position, preferentially ortho to a halogen substitutent. Methyl substituents exert no directing effect, and addition may even take place at substituted ring carbons. In all cases products with the added hydrogen(or deuterium) atom exo(as in 11) were obtained. These compounds were stable oils suitable for chromatographic purification and mass spectra analysis. Treatment of these with reagents designed to liberate the cyclohexadienyl ligand has not been investigated; nor has the further ligand exchange of compounds such as 11 with arenes been examined although this process may well lead to the interesting cation system 12.[23]



12

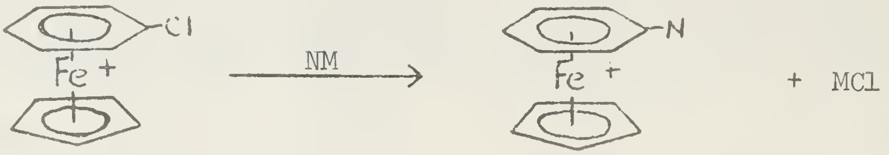


13

Polarograms of π-arene(π-cpd)iron(II) cations[24,25,26] confirmed the above observations. Thus, no oxidation was seen up to the dischange of the electrolyte for cations or dications in CH_3CN. A reversible, pH independent one-electron wave appeared at ca. -1.3 v, and an irreversible, pH dependent one-electron wave appeared at ca. -2.2 v, (versus s.c.e.) (cf. Scheme II). The exact $E_{\frac{1}{2}}$ value correlated well with σ_p^o [25] indicating that substituents on either ring ligand could transmit inductive components to the iron atom. For example, phenylmesitylene-bis((π-cpd)iron(II))$^{2+}$ has two reversible waves at -1.13 v and -1.50 v for the sequential reduction of the two iron centers.[27]

Perhaps the most interesting and synthetically useful reaction involving π-arene(π-cpd)iron(II) cations is the facile nucleophilic displacement of chlorine in compounds 1h and 13.[28,29] Under mild conditions (55°, 0.5 hr)

Table III. Examples of the Facile Nucleophilic Displacement of the Chlorine Atom in Chlorobenzene(π-cpd)iron(II) Cation.



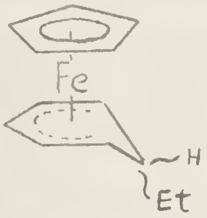
14

	NM	Conditions	Yield(%)	Decomposition Temperature(°C)[a]
14a.	EtONa	55°	72	217-218
	EtOH	EtOH/Na_2CO_3, 60°, 12 hr	76	
14b.	PhONa	acetone, 50°, 0.5 hr	82	221-222
14c.	PhSNa	ethanol, 50°, 0.3 hr	88	231.5-233
14d.	n-BuSNa	ethanol, 50°, 0.3 hr	89	187.5-188.5[b]
14e.	NH_3	sealed tube, 80°, 5 hr	95	193.5-195 ($^-BF_4$ s

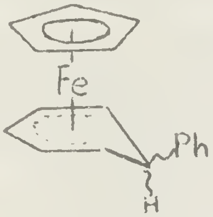
[a] -BPh_4 [b] Melting point

ethoxide ion in ethanol displaces chlorine giving 14a in high yield. Table III lists other nucleophiles and the products obtained. Kinetic studies[30] show the chlorine atom on 1h to be very highly activated, ca. 3 times as susceptable to displacement as that of 2,4-dinitrochlorobenzene and ca. 50 times as mobile as the fluorine atom of fluorobenzenechromium tricarbonyl.[31] The chlorine atom of 13 is also active, ca. 100 times as active as the chlorine atom of p-nitrochlorobenzene (or ca. 1/300th as active as that of 2,4-dinitrochlorobenzene). Sample basic hydrolysis of 1h leads to extensive decomposition without isolation of the expected phenol, 14(N=OH).

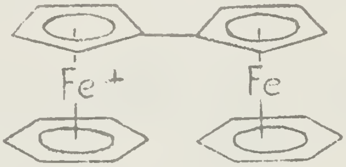
Powerful nucleophiles cause π-arene(π-cpd)iron(II) cations to disproportionate.[32] Thus treatment of a number of cations with $NaNH_2$, Na, sodium naphthalide,[33] EtLi, t-BuLi, and EtMgBr gave fair yields of ferrocene and freed arene as well as iron salts. This same dispropportionation occurs photochemically[34] with, apparently, good yields of the freed arene. In three reported instances use of a lithium reagent lead to addition to the arene ligand. Disproportionation of 1a with EtLi[3] and PhLi[22] gave, in part 15 and 16 respectively.



15



16



17

CONCLUSION

When the techniques of side chain oxidation and nucleophilic displacement are combined with well-known synthetic functional group transformations, a wide variety of substituted π-arene(π-cpd)iron(II) cations can be generated from the products of the ligand exchange reaction of arenes with ferrocene and substituted ferrocenes.[35, 36, 37] These cations have already contributed to the understanding of the electronic nature of the aromatic ring-metal bond[4] and have allowed the study (although not yet the isolation) of mixed Fe(II)-Fe(I) compound such as 17.[27]

Finally, development of mild, high yield reactions for cleaving the arene ring-iron π-bond may give the organic chemist a valuable tool for the synthesis of substituted aromatic systems.[38]

BIBLIOGRAPHY

1. T. H. Coffield, V. Sandel and R. D. Closson, J. Amer. Chem. Soc., 79, 5826 (1957).
2. A. N. Nesmayanov, N. A. Vol'kenau and I. N. Bolesova, Dokl. Akad. Nauk SSSR, 149, 615 (1963); Tetrahedron Lett., 1725 (1963).
3. A. N. Nesmayanov, Advan. Organometal. Chem., 10, 44 (1972).
4. D. N. Slocum and C. R. Ernst, Advan. Organometal. Chem., 10, 79 (1972).
5. A. N. Nesmayanov, N. A. Vol'kenau and I. N. Bolesova, Dokl. Akad. Nauk SSSR, 166, 607 (1966); Proc. Acad. Sci. USSR, Chem., 166, 116 (1966).
6. I. U. Khand, P. L. Pauson and W. E. Watts, J. Chem. Soc. C, 2261 (1968).
7. I. U. Khand, P. L. Pauson and W. E. Watts, J. Chem. Soc. C, 2257 (1968).
8. A. N. Nesmayanov, I. F. Leshchova, Yu. A. Ustynyuk, Ye. I. Sirotkina, I. N. Bolesova, L. S. Isayeva and N. A. Vol'kenau, J. Organometal. Chem., 22, 689 (1970).
9. D. Astruc and R. Dabard, C. R. Acad. Sci. Ser. C, 272, 1337 (1971).
10. A. N. Nesmayanov, E. I. Fedin, L. A. Fodorov and P. V. Petrovski, Zh. Strukt. Khim. SSSR, 13, 1033 (1972); J. Struct. Chem., 13, 964 (1972).
11. W. H. Morrison, Jr., E. Y. Ho and D. N. Hendrickson, J. Amer. Chem. Soc., 96, 3603 (1974).
12. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Shilovtseva, Dokl. Akad. Nauk SSSR, 160, 1327 (1965); Proc. Acad. Sci. USSR, Chem., 160, 203 (1965).
13. a) D. N. Slocum, S. P. Tucker and T. R. Engelmann, Tetrahedron Lett., 621 (1970); b) D. E. Bublitz, Can. J. Chem., 42, 2381 (1964).

14. C. C. Lee, R. G. Sutherland and B. J. Thomson, J. Chem. Soc., Chem. Commun., 907 (1972).
15. D. N. Hendrickson, private communication.
16. The properties of this compound are to be published in a forthcoming paper.
17. A. N. Nesmayanov, N. A. Vol'kenau and E. I. Sirotkina, Izv. Akad. Nauk, SSSR, Ser. Khim., 1170 (1967); Bull. Acad. Sci. USSR, Div. Chem. Sci., 1142 (1967).
18. E. I. Sirotkina, N. A. Vol'kenau and A. N. Nesmayanov, Izv. Akad. Nauk SSSR, Ser. Khim., 1605 (1969); Bull. Acad. Sci. USSR, Div. Chem. Sci., 1488 (1969).
19. A. N. Nesmayanov, N. A. Vol'kenau, I. N. Bolesova and L. S. Isaeva, Izv. Akad. Nauk SSSR, Ser. Khim., 2416 (1968); Bull Acad. Sci. USSR, Div. Chem. Sci., 2296 (1968).
20. A. N. Nesmayanov, N. A. Vol'kenau, L. S. Shilovtsova and V. A. Petrakova, J. Organometal. Chem., 61, 329 (1973).
21. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Shilovtsova, Izv. Akad. Nauk SSSR, Ser. Khim., 1206 (1970); Bull. Acad. Sci. USSR, Div. Chem. Sci., 1153 (1970).
22. D. Jones, L. Pratt and G. Wilkinson, J. Chem. Soc. A, 4458 (1962); see also I. U. Uhand, P. L. Pauson and W. E. Watts, J. Chem. Soc. C, 2024 (1969) for evidence that structure 16 has an exo-phenyl.
23. J. F. Helling and D. M. Braitsch, J. Amer. Chem. Soc., 92, 7207 (1970).
24. R. E. Dessy, F. E. Stary, R. B. King and M. Waldrop, J. Amer. Chem. Soc., 88, 471 (1966).
25. A. N. Nesmayanov, L. I. Denisovich, S. P. Gubin, N. A. Vol'kenau, E. I. Sirotkina and I. N. Bolesova, J. Organometal. Chem., 20, 169 (1969).
26. D. Astruc, E. Laviron and R. Dabard, C. R. Acad. Sci. Ser. C, 269, 608 (1969).
27. W. H. Morrison, Jr., E. Y. Ho and D. N. Hendrickson, J. Amer. Chem. Soc., in press.
28. A. N. Nesmayanov, N. A. Vol'kenau and I. N. Bolesova, Dokl. Akad. Nauk SSSR, 175, 606 (1967); Proc. Acad. Sci. USSR, Chem., 175, 661 (1967).
29. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Isaeva, Dokl. Akad. Nauk SSSR, 176, 106 (1967); Proc Acad. Sci. USSR, Chem., 176, 772 (1967).
30. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Isaeva, Dokl. Akad. Nauk SSSR, 183, 834 (1968); Proc. Acad. Sci. USSR, Chem., 183, 1042 (1968).
31. M. C. Whiting, Chem. Weekbl., 59, 119 (1963).
32. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Shilovtseva, Izv. Akad. Nauk SSSR, Ser. Khim., 726 (1969); Bull. Acad. Sci. USSR, Div. Chem. Sci., 664 (1969).
33. A. N. Nesmayanov, N. N. Vol'kanau and L. S. Shilovtseva, Dokl. Akad. Nauk SSSR, 190, 354 (1970); Proc. Acad. Sci. USSR, Chem., 190, 51 (1970).
34. A. N. Nesmayanov, N. A. Vol'kenau and L. S. Shilovtseva, Dokl. Akad. Nauk SSSR, 190, 857 (1970); Proc. Acad. Sci. USSR, Chem., 190, 118 (1970).
35. A. N. Nesmayanov, N. A. Vol'kenau, E. I. Sirotkina and V. V. Deryabin, Dokl. Akad. Nauk SSSR, 177, 1110 (1967); Proc. Acad. Sci. USSR, Chem., 177, 1170 (1967).
36. A. N. Nesmayanov, N. A. Vol'kenau, and L. S. Isaeva, Dokl. Akad. Nauk SSSR, 183, 606 (1968); Proc. Acad. Sci. USSR, Chem., 183, 1026 (1968).
37. E. I. Sirotkina, A. N. Nesmayanov and N. A. Vol'kenau, Izv. Akad. Nauk SSSR, Ser. Khim., 1524 (1969); Bull. Acad. Sci. USSR, Div. Chem. Sci., 1413 (1969).
38. One as yet undeveloped possibility is the reaction of arene(π-cpd)iron(II) cations with β-diketones. See A. V. Pavlycheva, G. A. Razuvaev and O. N. Suvorova, Dokl. Acad. Nauk SSSR, 184, 105 (1969).

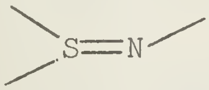
SULFILIMINE CHEMISTRY

Reported by Karl Wiegers   November 4, 1974

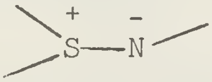
INTRODUCTION

Sulfilimines,[1] also referred to as iminosulfuranes, sulfinimines, and sulfimides, are a class of ylides containing a formal sulfur-nitrogen double bond. A variety of substituents may be present on both the sulfur and the nitrogen atoms. Most common are sulfilimines with alkyl or aryl groups bonded to sulfur, and acyl or sulfonyl functionalities on nitrogen, although N-aryl, N-alkyl, and N-unsubstituted ("free") sulfilimines are also known.

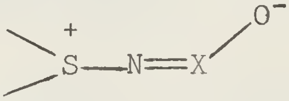
The sulfur-nitrogen bond is thought to be semi-polar in nature, resembling the S-O bond in sulfoxides, and two major canonical forms (1 and 2) contribute to the bond representation. The presence of resonance electron-withdrawing substituents on nitrogen (acyl, sulfonyl) decreases the contribution of the ylene structure, and stabilizes the sulfilimine by additional charge delocalization (3).



1 (ylene)



2 (ylide)



3 (betaine)

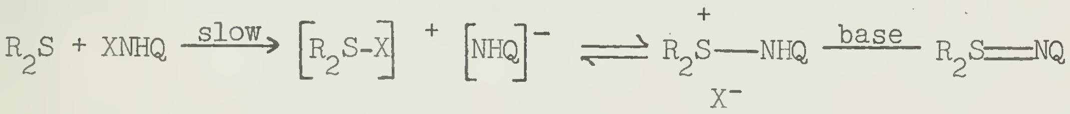
X = C,S

This seminar will present several of the approaches commonly used in the preparation of sulfilimines, and will discuss the nature of the sulfur-nitrogen bond. The reactivity of the S=N linkage will be illustrated by several typical reactions of sulfilimines.

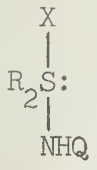
PREPARATIVE METHODS

The most common approach to sulfilimine synthesis involves treatment of a sulfide with a positive-halogen donor, forming an intermediate halosulfonium cation, which can then react with a nitrogen nucleophile. The sulfonium salt thus formed is converted into the corresponding sulfilimine upon treatment with a base, such as aqueous alkali or triethylamine in chloroform. This method is illustrated in general form in Scheme I. While the intermediacy of a neutral tetracovalent sulfurane (4) has not been explicitly suggested for these reactions, it is entirely possible that such a species may indeed have transient existence, either as a true intermediate or as a transition state.

Scheme I

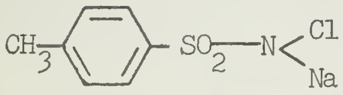


$$R_2S + XNHQ \xrightarrow{\text{slow}} [R_2S\text{-}X]^+ \ [NHQ]^- \rightleftharpoons R_2\overset{+}{S}\text{—}NHQ \ X^- \xrightarrow{\text{base}} R_2S{=}NQ$$



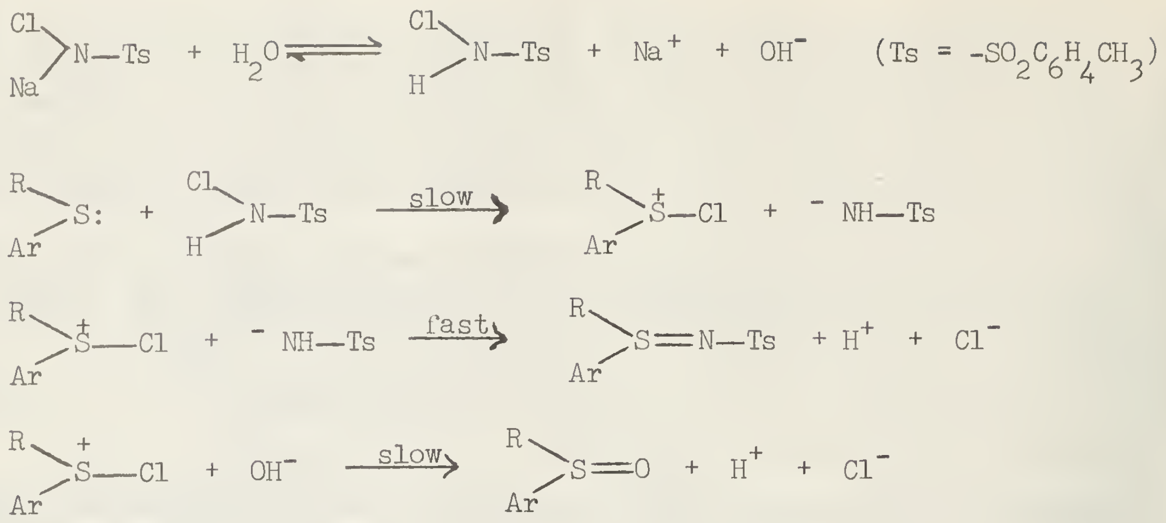
4

This method was first used by Mann and Pope[2] in the preparation of S,S-dialkyl-N-tosylsulfilimines by the reaction between dialkyl sulfides and Chloramine T (sodium N-chloro-*p*-toluenesulfonamide, 5) in water. This approach has been studied and modified by Oae and co-workers.[3] The reaction is first-order both in sulfide and in Chloramine T, and it is strongly pH-dependent in aqueous methanol, reaching a maximum rate at about pH 5. The mechanism is believed to consist of the sequence shown in Scheme II. That the rate-determining step involves nucleophilic attack by sulfur is supported by the observation that electron-donating groups on Ar promote the reaction (ρ = -0.94).

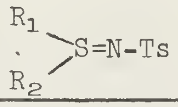


5

Scheme II



Because of the side reaction forming sulfoxide, Tsujihara, et al.,[3] showed that optimum synthetic conditions were obtained by reacting the sulfide and Chloramine T in methanol in the presence of a small amount of acetic acid, followed by quenching in dilute aqueous sodium hydroxide. Under these conditions, excellent yields of dialkyl, aryl alkyl, and diaryl N-tosylsulfilimines are realized (Table 1). These sulfilimines are stabilized by the presence of the sulfonyl functionality, and are crystalline compounds which are water-soluble and hydrolyze slowly to the corresponding sulfoxide and sulfonamide.

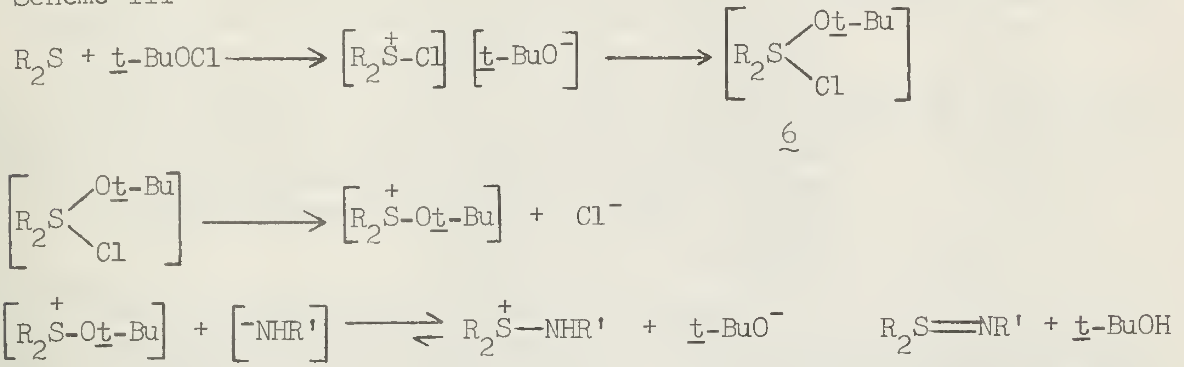
Table 1. N-Tosylfulfilimines,  $R_1R_2S{=}N\text{-}Ts$ (ref. 3)

R_1	R_2	Mp, °C	Yield,%
CH_3	CH_3	157-157.5	90
$(CH_3)_2CH$	$(CH_3)_2CH$	117-118	95
CH_3	C_6H_5	129-130	90
C_6H_5	C_6H_5	111-112	94
$-(CH_2)_4-$		145-146	87

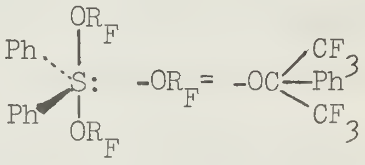
A variety of other N-substituted sulfilimines can be synthesized by the reaction of sulfides with appropriate halogen donors and nitrogen nucleophiles. N-acetylsulfilimines and N-carbethoxysulfilimines have been prepared using N-bromoacetamide[5,6] and N-chlorocarbamate ($ClNHCO_2C_2H_5$),[7] respectively, in good to excellent yields. Basic work-up in these reactions has employed triethylamine in chloroform.[5-7] Similarly, N-chlorourea has been used in the preparation of N-carbamoylsulfilimines from aryl alkyl sulfides.[8]

A more general method for the synthesis of a variety of N-substituted sulfilimines is that of Swern, Ikeda, and Whitfield,[9] who treated sulfides with t-butylhypochlorite, followed by one of several substituted sodium amide species. In reactions carried out between -50° and -60°, sulfilimines with SO_2Ph, CN, COPh, $COCH_3$, $COCH_2Cl$, and $COCHCl_2$ groups on N can be prepared in 40-80% crude yield. The procedure is most effective for moderately acidic amides, such as $PhSO_2NH_2$ and NH_2CN. The mechanism in Scheme III was proposed; the sulfurane intermediate 6 has been shown to exist in independent experiments, including trapping experiments and low-temperature nmr studies. While this mechanism is plausible and consistent with the experimental evidence, the participation of ionic intermediates cannot be ruled out.

Scheme III

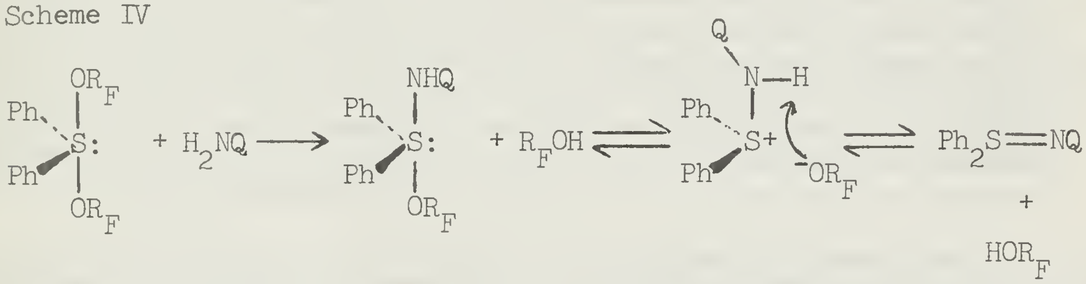


A novel synthesis of S,S-diarylsulfilimines has recently been reported by Franz and Martin,[10,11] who reacted primary amine derivatives with the diphenyldialkoxysulfurane 7 in chloroform, methylene chloride, or ether. Reaction of the sulfurane with ammonia, primary amines, primary amides, anilines, or primary sulfonamides leads to N-H, N-alkyl, N-acyl, N-aryl, or N-sulfonylsulfilimines, respectively, in moderate to high yields.[11] This is the only reported general method of preparation of the highly reactive N-alkylsulfilimines. The reaction is thought to proceed *via* the mechanism outlined in Scheme IV.



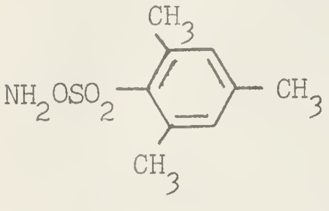
7

Scheme IV



The formation of sulfilimines by condensation of amines with activated sulfoxides [12,13] has recently been examined and extended by Swern, *et al.*[14,15] These workers found that the activation of dimethylsulfoxide by electrophiles such as SO_3, P_4O_{10}, and acetic anhydride leads to the formation of intermediates which react readily with sulfonamides, carboxamides, and anilines to give sulfilimines in good yield. Thus, the new synthetic approaches introduced by Martin[11] and Swern[15] permit the straightforward preparation of a wide variety of substituted sulfilimines.

Free sulfilimines are highly reactive species, and thus are difficult to isolate in pure form.[16,17] A useful preparation has been developed by Tamura and co-workers,[18,19] who combined diaryl or aryl alkyl sulfides with MSH (O-mesitylenesulfonylhydroxylamine, 8) in ethanol at 0°. The resulting sulfonium mesitylenesulfonate salt was then passed through an anion exchange resin in the OH^- form to afford an alcoholic solution of free sulfilimine. An alternative method is that of Furukawa, et al.,[20] which consists of dissolving N-tosylsulfilimines in concentrated sulfuric acid, followed by quenching in ice or cold ether. Neutralization and extraction afford the sulfilimine monohydrate.



8

Okahara and Swern[21] and Hayashi and Swern[22,23] have reported that the thermolysis[21] or photolysis[22,23] of nitrene precursors in dimethylsulfide solution leads to the formation of sulfilimines in modest yields. Photolysis of ethyl azidoformate ($N_3CO_2C_2H_5$)[22] or benzoyl azide[23] resulted in the formation of 28% of S,S-dimethyl-N-carbethoxysulfilimine and 38% of S,S-dimethyl-N-benzoylsulfilimine, respectively. The nitrenes derived from these azido compounds have been shown to be largely singlet nitrene,[22,23] and sulfides are known to be highly efficient traps for singlet nitrenes.[24]

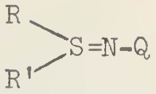
A recent, unique synthesis of sulfilimines has been reported by Shine and Kim,[25,26] who found that thianthrene cation radical perchlorate can be trapped by amines to form sulfilimines in quantitative yields.

SULFUR-NITROGEN BONDING

A sizeable body of evidence has been collected in efforts to understand the relative contributions of ylide, ylene, and betaine structures to the S-N bond in sulfilimines. The X-ray crystal structure of S,S-dimethyl-N-tosylfulfilimine shows[27] that the sulfilimine sulfur atom is tetrahedral, and that both of the sulfur-nitrogen bonds are shorter than S-N single bonds by 0.1-0.15 Å, implying appreciable $d\pi$ - $p\pi$ bonding. Extended HMO calculations on N-sulfonylsulfilimines have suggested[28-30] that the $d\pi$ - $p\pi$ bonding system is delocalized over both the sulfilimine (S^{IV}) and sulfonyl (S^{VI}) sulfur atoms, and that the $N-S^{VI}$ bond is stronger than the $N-S^{IV}$ bond. Interestingly, the calculated bond order for the $N-S^{IV}$ bond is virtually independent of the angle of rotation about the bond, although the conformer energies vary as expected. This result suggests that observed rotational barriers are primarily due to steric interactions[28,29] or to repulsions between the lone pairs of electrons on sulfur and nitrogen.[31]

Infrared spectroscopy has proved to be a valuable tool in the investigation of sulfilimine bonding. The S-N stretching band is normally observed in the region between 770 and 1130 cm^{-1}; variations within this range reflect the bond order of the S-N bond, in that shifts to higher frequencies imply more S-N double-bond character. Table 2 summarizes the regions of the infrared spectrum in which common N-substituted sulfilimines absorb. Note that the shifts in frequency relative to those for unsubstituted sulfilimines are qualitatively those expected on the basis of the inductive and conjugative

Table 2. Infrared S-N stretching frequencies of sulfilimines,



Q	ν_{SN}, cm^{-1}	method	ref.
alkyl	1060-1130	CCl_4	11
$CONH_2$	960-1039	KBr	8
$SO_2C_6H_4CH_3$-p	930-987	KBr, $CHCl_3$[a]	30-33
Aryl	890-990	CCl_4	11,15
H (S,S-diphenyl)	910	CCl_4	11
Acyl	770-840	KBr,liq. film	5,15
$CO_2CH_3CH_3$	782	liq.film	7

[a] Difference between frequencies in $CHCl_3$ solution and in a KBr pellet is ca. 10 cm^{-1} or less

characteristics of the N-substituents. The striking increase in frequency observed with alkyl substituents has been attributed[11] to the electron-donating inductive nature of alkyl groups, which leads to an increase in the importance of the ylene contributor relative to that of the ylide.

The effect of R and R' groups bonded to sulfur has also been examined, and it is found that S-methyl groups lead to a decreased S-N stretching frequency. This phenomenon has been explained by invoking a hyperconjugative interaction, which enhances the stability of the ylide form.[32,35]

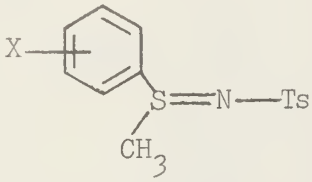
The frequencies of carbonyl infrared absorptions in N-acylsulfilimines illustrate the significance of the betaine structure 3. In the cases of N-carbamoyl-,[8] N-carbethoxy-,[7] and N-acetylsulfilimines,[5] the carbonyl band appears at substantially lower frequency than in the parent amide, implying lower C-O bond orders in the delocalized sulfilimine structures. A similar effect is observed with N-sulfonylsulfilimines.[15] Also of interest are the observations that the carbonyl frequency undergoes a decrease of 105-120 cm^{-1} for N-carbethoxy-[7] and 135-140 cm^{-1} for N-acetyl[5b] substituents upon conversion of the sulfonium halides into the corresponding sulfilimines. These data suggest that the betaine structure is the most important contributing form in N-acetyl- and N-carbethoxysulfilimines,[5b,7] although Oae, Masuda, Tsujihara, and Furukawa[8] believe that the ylide is the major contributor in N-carbamoylsulfilimines.

The ultraviolet spectra of N-acyl-,[7] N-sulfonyl-,[36] and N-unsubstituted[19] sulfilimines exhibit λ_{max} between 215 and 240 nm, which has been interpreted to mean that the ylene structure does indeed make a contribution to sulfilimine bonding, but the low values of ϵ_{max} observed suggest that the ylene contribution is much smaller than that of the ylide or betaine forms.[7] In addition, the conversion of S,S-dialkyl-N-acylsulfonium salts into sulfilimines leads to upfield shifts of 0.6-1.2 ppm[5,7] in the nmr signals of methyl or methylene protons bonded to the sulfur atom, showing that the positive charge on sulfur is being decreased by bonding of the ylene or ylide type.

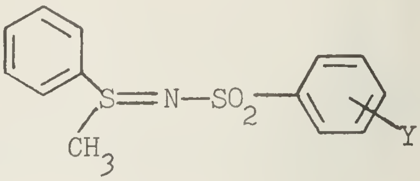
POLAR REACTIONS OF THE S-N BOND

The semi-polar nature of the sulfur-nitrogen bond in sulfilimines should result in substantial nucleophilic character at nitrogen and electrophilic character at sulfur. These predictions are substantiated by a variety of reactions, including hydrolysis to the sulfoxide and ammonia derivative, and reactions with various electrophiles to form new nitrogen-carbon bonds.

Kapovits, Ruff, and Kucsman[37] have examined the basicity of the substituted sulfilimines 9 and 10 in aqueous sulfuric acid; concentrations of



9



10

protonated and unprotonated species were measured by ultraviolet spectrophotometry. The sulfilimines were found to be Hammett bases, and calculation of pK_a's from the acidity function yielded values between -1.8 and -3.0, indicating that these sulfilimines are weaker bases than pyridine and sulfoxamines, but stronger than sulfonamides.

Stable sulfilimines hydrolyze only slowly in pure water, whereas N-alkyl and free sulfilimines are rapidly converted into the corresponding sulfoxide and amine or amide.[11,17,20] The hydrolysis of all sulfilimines is facile in both acidic and basic media,[5,8,38] and hydroxide ion particularly promotes the reaction. Day and Cram[39] found that the alkaline hydrolysis of optically pure S-(p-tolyl)-S-methyl-N-tosylsulfilimine results in inversion of configuration at the formally tricoordinate sulfur atom caused by attack of $OH^{\ominus}$ at this electrophilic center. The hydrolysis of N-tosylsulfilimines in aqueous sulfuric or perchloric acid has been shown by Kapovits, Ruff, and Kucsman[38] to involve initial rapid protonation at nitrogen, followed by rate-determining attack of water on the sulfonium ion formed.

The reactivity of the sulfur-nitrogen bond is further exemplified by the reaction of sulfilimines with various electrophiles. Franz and Martin[11] have shown that S,S-diaryl-N-alkylsulfilimines can be acylated rapidly with acyl halides at -20 to -40°, and that alkylation at nitrogen can be effected in 90% yield by dissolution in excess methyl iodide. The alkylation of the more stable N-tosylsulfilimines requires the use of highly reactive alkylating agents such as triethyloxonium fluoroborate.[11,40,41] Stabilized sulfilimines exhibit markedly attenuated nucleophilicity, as evidenced by the report[7] that S,S-dialkyl-N-carbethoxysulfilimines fail to react with electrophiles such as acrylonitrile and ethyl acrylate.

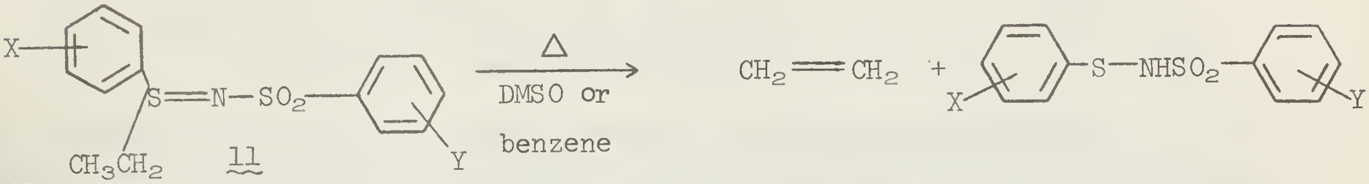
The free diphenyl and phenyl methyl sulfilimines prepared by Tamura and co-workers[19] are acylated rapidly and in high yield upon treatment with acetyl chloride, acetic anhydride, ethyl chloroformate, or phenyl isocyanate. These reactive sulfilimines were also observed to undergo Michael addition to substrates such as benzoyl acetylene, followed by ring closure to the isoxazole, and addition to 1,4-dienones to yield up to 90% of the aminated product.

THERMAL REACTIONS

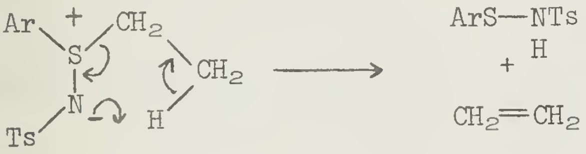
Oae and co-workers[42-45] have extensively studied the thermal elimination of S,S-dialkyl-N-tosylsulfilimines to olefins and the parent sulfenamide; the presence of β-hydrogen atoms on at least one S-alkyl group is required.

Good yields of olefins are realized when the sulfilimines are heated at 100-130° neat or in benzene or DMSO.

Substituted S-aryl-S-ethyl-N-arylsulfonylsulfilimines such as **11** were examined in detail.[45] The reaction followed first-order kinetics, and Hammett plots using σ_p values for substituents X and Y were linear with $\rho_X = +0.90$ in benzene and $+0.95$ in DMSO, and $\rho_Y = -0.60$ in benzene. The reaction is faster in benzene by approximately an order of magnitude; this observation was attributed[45] to strong dipolar solvation of the sulfilimine S-N bond by the S-O group in DMSO. These and other kinetic data, including the observation of a substantial deuterium kinetic isotope effect for the beta hydrogen atoms, led Oae, *et al.*, to postulate that the thermal elimination of olefins from sulfilimines proceeds *via* a concerted mechanism, passing through a five-membered transition state (Scheme V). Demonstration of the high *cis* stereospecificity of the elimination led these investigators to propose[44] that the reaction may be useful for the stereospecific formation of olefins in better than 80% yields from appropriately substituted S-alkylsulfilimines.



Scheme V



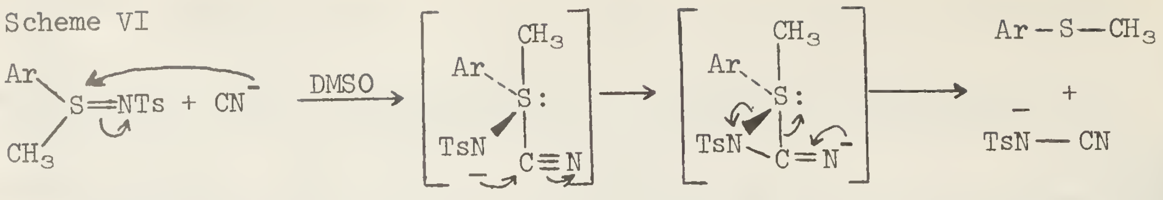
Other N-substituted sulfilimines have also been observed to undergo olefin elimination upon heating,[7,8,46] but S,S-dialkyl-N-acetyl-[46] and N-carbethoxysulfilimines[7] also yield a variety of products formed by ionic pathways. Other thermolytic reactions of sulfilimines include the rearrangement of S,S-dimethyl-N-arylsulfilimines to *o*-methylthiomethylanilines,[47] and rearrangement of S,S-diallyl-N-tosylsulfilimines to S-allyl-N-allyl-N-tosylsulfenamides.[32] Sulfilimines have also been heated in DMSO solution to yield 70-90% of unsymmetrical disulfides, presumably *via* a polar mechanism, since aldehydes were formed nearly quantitatively.[48] This reaction has possible synthetic utility in the formation of such disulfides.

REDUCTION TO SULFIDES

The reduction of sulfilimines to the parent sulfides illustrates both the lability of the sulfur-nitrogen bond and the electrophilic character at the sulfur atom. McCall, Tarbell, and Havill[49] showed that N-tosylsulfilimines are readily reduced to the corresponding sulfides in good yields by hydrogenation over 5% palladium on charcoal.

The reduction of N-tosylfulfilimines by several nucleophiles, including cyanide ion,[51,53] phenyl magnesium bromide,[50] triphenylphosphine,[51,52] thiophenol,[53,54] and iodide ion[54] has been studied. The reactions were carried out in DMF, DMSO, or methanol solution, and resulted in up to 100% yields of sulfides. The reaction with cyanide ion was examined in detail by Oae, Aida, and Furukawa,[53] and a wide range of kinetic data was collected. The reduction is first-order in each component, and cyanide ion was shown to react stoichiometrically, rather than catalytically. The reaction is slowed by steric hindrance about the sulfur atom. The kinetic data suggested that the reaction can be considered to involve backside attack by cyanide ion on sulfur, followed by internal rearrangement and simultaneous loss of both the N-tosyl functionality and the leaving group (Scheme VI).[53]

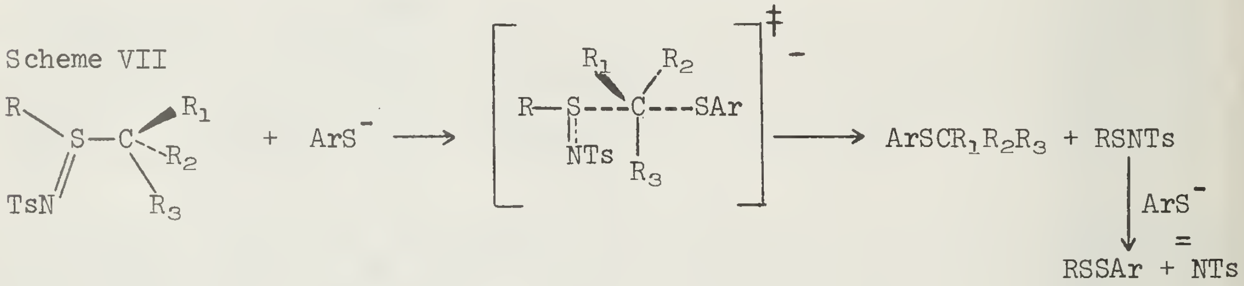
Scheme VI



The hydrolysis product of TsN-CN, N-tosylurea, was also isolated in good yield upon aqueous work-up, lending further credence to this proposed pathway. Similar mechanisms are postulated for the reductions by PPh_3, I^-, and SCN^-.[53] However, the formation of disulfides concurrent with the reduction process when thiophenol is used suggests that this reaction must involve two molecules of the nucleophile.[54]

These reduction mechanisms have been rationalized, although not entirely satisfactorily, on the basis of the hard-soft acid-base (HSAB) theory.[53] According to this explanation, soft bases such as CN^-, PPh_3, and ArSH will preferentially attack the tricoordinate sulfur atom to form a tetravalent intermediate, which leads to the reduction process. In contrast, harder nucleophiles (OH^-, OR^-, N_3^-) may attack either at sulfur or at a benzylic carbon atom alpha to sulfur, giving a more complicated reaction. However, this explanation is not consistent with the observation that sulfilimines are readily attacked by hydroxide ion at sulfur to yield the sulfoxide. Additional complications are presented by the report by Aida, Furukawa, and Oae[55] that the reaction of S,S-dialkyl-N-tosylsulfilimines with thiophenolate ion in DMF results in substitution on the α-carbon (Scheme VII).

Scheme VII



The rationalization of the reaction in Scheme VII by the HSAB theory is probably not as reasonable as supposing that the steric hindrance about the sulfur atom directs the bulky thiophenolate nucleophile to attack at the less hindered carbon atom.

SUMMARY

A number of different synthetic approaches to substituted sulfilimines exists; reaction of sulfides with Chloramine T is the most commonly used method. Two general synthetic routes have recently been reported by Franz and Martin[11] and by Varkey, Whitfield, and Swern.[15] Sulfilimines are useful models for the investigation of sulfur-nitrogen bonding mechanisms. The S-N linkage undergoes a variety of concerted and polar reactions. Sulfilimines have limited synthetic utility as aminating agents and as precursors to olefins.

BIBLIOGRAPHY

1. B. H. Nicolet and J. Willard, Science, 53, 217 (1921).
2. F. G. Mann and W. J. Pope, J. Chem. Soc., 121, 1052 (1922).
3. K. Tsujihara, N. Furukawa, K. Oae, and S. Oae, Bull. Chem. Soc. Jap., 42, 2631 (1969).

4. Á. Kucsman, I. Kapovits, and M. Balla, Tetrahedron, 18, 75 (1962).
5. (a) H. Kise, G. F. Whitfield, and D. Swern, J. Org. Chem., 37, 1121 (1972).
   (b) H. Kise, G. F. Whitfield, and D. Swern, Tetrahedron Lett., 1761 (1971).
6. M. V. Likhosherstov, Zh. Obshch. Khim., 17, 1478 (1947).
7. G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, J. Org. Chem., 39, 2148 (1974).
8. S. Oae, T. Masuda, K. Tsujihara, and N. Furukawa, Bull. Chem. Soc. Jap., 45, 3586 (1972).
9. D. Swern, I. Ikeda, and G. F. Whitfield, Tetrahedron Lett., 2635 (1972).
10. J. A. Franz and J. C. Martin, J. Amer. Chem. Soc., 95, 2017 (1973).
11. J. A. Franz and J. C. Martin, J. Amer. Chem Soc., in press.
12. P. Claus and W. Vycudilik, Tetrahedron Lett., 3607 (1968).
13. D. S. Tarbell and C. Weaver, J. Amer. Chem. Soc., 63, 2939 (1941).
14. A. K. Sharma and D. Swern, Tetrahedron Lett., 1503 (1974).
15. (a) T. E. Varkey, G. F. Whitfield, and D. Swern, Int. J. Sulfur Chem., Part A, 1, 126 (1971).
    (b) T. E. Varkey, C. F. Whitfield, and D. Swern, J. Org. Chem., in press.
16. R. Appel, W. Büchner, and E. Guth, Justus Liebigs Ann. Chem., 618, 53 (1958).
17. R. Appel and W. Büchner, Chem. Ber., 95, 849, 855 (1962).
18. Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, Tetrahedron Lett., 4137 (1972).
19. Y. Tamura, K. Sumoto, H. Matsushima, H. Taniguchi, and M. Ikeda, J. Org. Chem., 38, 4324 (1973).
20. N. Furukawa, T. Omata, T. Yoshimura, T. Aida, and S. Oae, Tetrahedron Lett., 1619 (1972).
21. M. Okahara and D. Swern, Tetrahedron Lett., 3301 (1969).
22. Y. Hayashi and D. Swern, Tetrahedron Lett., 1921 (1972).
23. Y. Hayashi and D. Swern, J. Amer. Chem. Soc., 95, 5205 (1973).
24. W. Ando, N. Ogino, and T. Migita, Bull. Chem. Soc. Jap., 44, 2278 (1971).
25. H. J. Shine and K. Kim, Tetrahedron Lett., 99 (1974).
26. K. Kim and H. J. Shine, J. Org. Chem., 39, 2537 (1974).
27. A. F. Cameron, N. J. Hair, and D. G. Morris, Chem. Comm., 918 (1971).
28. P. Mezey and Á. Kucsman, Chem. Comm., 1448 (1971).
29. P. Mezey and Á. Kucsman, J. C. S. Faraday II, 68, 2060 (1972).
30. Á. Kucsman, A. Kalman, and I. Kapovits, Acta Chim. Acad. Sci. Hung., 53, 97 (1967).
31. G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, Tetrahedron Lett., 3543 (1970).
32. Á. Kucsman, F. Ruff, and I. Kapovits, Tetrahedron, 22, 1575 (1966).
33. K. Tsujihara, N. Furukawa, and S. Oae, Bull. Chem. Soc. Jap., 43, 2153 (1970).
34. Á. Kucsman, I. Kapovits, and F. Ruff, Acta Chim. Acad. Sci. Hung., 40, 75 (1964).
35. Á. Kucsman, I. Kapovits, and F. Ruff, ibid., 54, 153 (1967).
36. Á. Kucsman, F. Ruff, and I. Kapovits, ibid., 50, 325 (1966).
37. I. Kapovits, F. Ruff, and Á. Kucsman, Tetrahedron, 28, 4413 (1972).
38. I. Kapovits, F. Ruff, and Á. Kucsman, Tetrahedron, 28, 4405 (1972).
39. J. Day and D. J. Cram, J. Amer. Chem. Soc., 87, 4398 (1965).
40. C. R. Johnson, J. J. Rigau, M. Haake, D. McCants, Jr., J. E. Keiser, and A. Gertsema, Tetrahedron Lett., 3719 (1968).
41. C. R. Johnson and J. J. Rigau, J. Org. Chem., 33, 4340 (1968).
42. S. Oae, K. Tsujihara, and N. Furukawa, Tetrahedron Lett., 2663 (1970).
43. S. Oae, K. Harada, K. Tsujihara, and N. Furukawa, Bull. Chem. Soc. Jap., 46, 3482 (1973).
44. K. Tsujihara, K. Harada, N. Furukawa, and S. Oae, Tetrahedron, 27, 6101 (1971).

45. K. Tsujihara, N. Furukawa, and S. Oae, Tetrahedron, 27, 4921 (1971).
46. H. Kise, G. F. Whitfield, and D. Swern, J. Org. Chem., 37, 1125 (1972).
47. P. Claus and W. Reider, Monatshefte Chem., 103, 1163 (1972), and references cited therein.
48. K. Tsujihara, T. Aida, N. Furukawa, and S. Oae, Tetrahedron Lett., 3415 (1970).
49. M. A. McCall, D. S. Tarbell, and M. A. Havill, J. Amer. Chem. Soc., 73, 4476 (1951).
50. S. Oae, T. Yoshimura, and N. Furukawa, Bull. Chem. Soc. Jap., 45, 2019 (1972).
51. S. Oae, T. Aida, K. Tsujihara, and N. Furukawa, Tetrahedron Lett., 1145 (1971).
52. T. Aida, N. Furukawa, and S. Oae, Chem. Lett., 805 (1973).
53. S. Oae, T. Aida, and N. Furukawa, Int. J. Sulfur Chem., 8, 401 (1973).
54. C. Dell'erba, G. Guanti, G. Gaini, and G. Garbarino, Gazz. Chim. Ital., 101, 890 (1971).
55. T. Aida, N. Furukawa, and S. Oae, Tetrahedron Lett., 4255 (1971).

STEREOCHEMICAL ELUCIDATION USING LANTHANIDE NMR SHIFT REAGENTS

Reported by David Sikkenga November 7, 1974

Lanthanide shift reagents(LSR) were introduced in 1969 by Hinckley,[1] who used them to improve the resolution of the nmr spectrum of cholesterol. Since that time, a variety of new shift reagents have been developed, and they have been very useful in structure determination by nmr.[2]

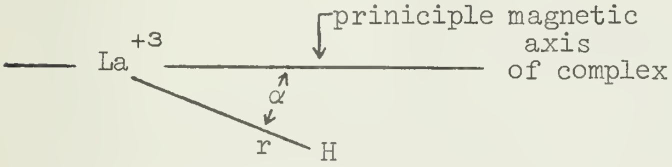
The general structure of LSRs involve a lanthanide(III) ion complexed by three β-diketonate ligands. Two of the most common shift reagents are tris(dipivalomethanato)europium(III), 1, and its heptafluoro derivative 2. In order to experience a shift, a substrate must contain a heteroatom with some degree of Lewis basicity permitting it to bind to a LSR. Strong Lewis bases such as alcohols, amines, carbonyls, epoxides, and sulfoxides interact strongly with LSRs, while weaker bases like ethers, sulfides, nitroalkanes, and nitriles interact weakly; non-basic olefins, aromatics, and halides do not interact at all.[3] In this interaction, the lanthanide ion expands its coordination sphere allowing the substrate to bind to it in a reversible manner. Complexed(shifted) and non-complexed(unshifted) substrate molecules are in rapid equilibrium so that an average shift is observed.

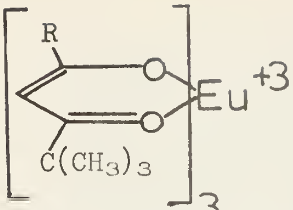
STEREOCHEMICAL ELUCIDATION

LSRs have been used in several different ways to aid in determination of stereochemistry. Since they shift protons of a molecule by different amounts, they often simplify complex spectra by spreading out the individual proton resonances. Yee and Bentrude have used 1 to resolve the spectrum of a phosphorinane, so that coupling constants could be measured directly from the resulting first order spectrum.[4] Mazzocchi made use of 1 to spread out the resonances of 3 to facilitate determination of coupling constants and to aid in decoupling experiments requiring separated resonances.[5] The relative amounts of cis-cis-, cis-trans-, and trans-trans-bis(4-aminocyclohexyl)methane were determined using characteristic peaks for each isomer revealed only in the presence of 1.[6]

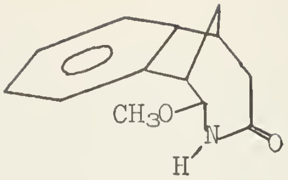
The LSR-substrate proton interaction has been shown to be mainly pseudocontact (through space) in nature.[2b,d,7] The equation relates the change in the chemical shift (ΔH) of a proton upon addition of a LSR, to the distance and angular terms illustrated in the figure. The equation has been used in different ways. Often it is simplified by neglecting the angular term. This is often done when the number of stereochemical possibilities is limited to two. The ΔH values of the two corresponding protons of the two structures are compared to the distances of these protons to the heteroatom. A larger ΔH implies shorter distances. This method has been used on cyclic esters[8] and a variety of oximes to determine syn or anti configurations.[9] The E and Z isomers of 3-chlorocyclobenzaprine were distinguished in the presence of 1, and the assignment confirmed by X-ray.[10] The geometrical isomers nerol and geraniol were also distinguished with the aid of 1.[11] Finally, the cis and trans-1-cyclohexyl-2-phenylazetidines 4 were identified by comparison of the ΔH of H_c of the two isomers.[12] In some cases, correlations have been made between the ΔH values and distances of all the protons to the heteroatom complexing to the LSR. The configuration of the epoxide 5 has been assigned in this way.[13] All the protons of cyclopentanol and a number of hydroxyadamantanes have been identified by measurements made in this manner.[14]

$$\Delta H = (\text{constant})\ (3\cos^2\alpha - 1)/r^3$$

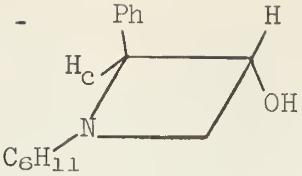




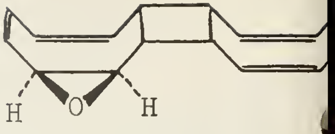
R= -C(CH$_3$)$_3$
R= -CF$_2$CF$_2$CF$_3$



3



4



5

Several workers have taken into account angle terms as well as the lanthanide-heteroatom distance in an attempt to obtain more accurate results. Rigid sulfoxides have been studied and stereochemistry assigned by Fraser.[15] Thioamides have also been studied in this manner.[16] Some α,β-unsaturated aldehydes of known stereochemistry were studied in the presence of a LSR to determine the La^{+3}-O-C angle. These values along with observed ΔH values were used to determine stereochemistry of other aldehydes.[17] Recently, a method has been described which used a computer program to calculate the best stereochemical structure given the ΔH values and the carbon skeleton of the molecule.[18]

Lanthanides containing chiral ligands have recently been used to distinguish enantiomers with nmr.[3,20] Goe used the tris(trifluoroacetylcamphorato)europium shift reagent to distinguish cis(meso) and trans(d,l) forms of dimethyl-3,3,4,4-tetramethylcyclobutane-1,2-dicarboxylate.[19] Some correlation between ΔH values and absolute configuration has been reported[21,22] but a good model of the interaction has not been formulated, making predictions of absolute configuration difficult

BIBLIOGRAPHY

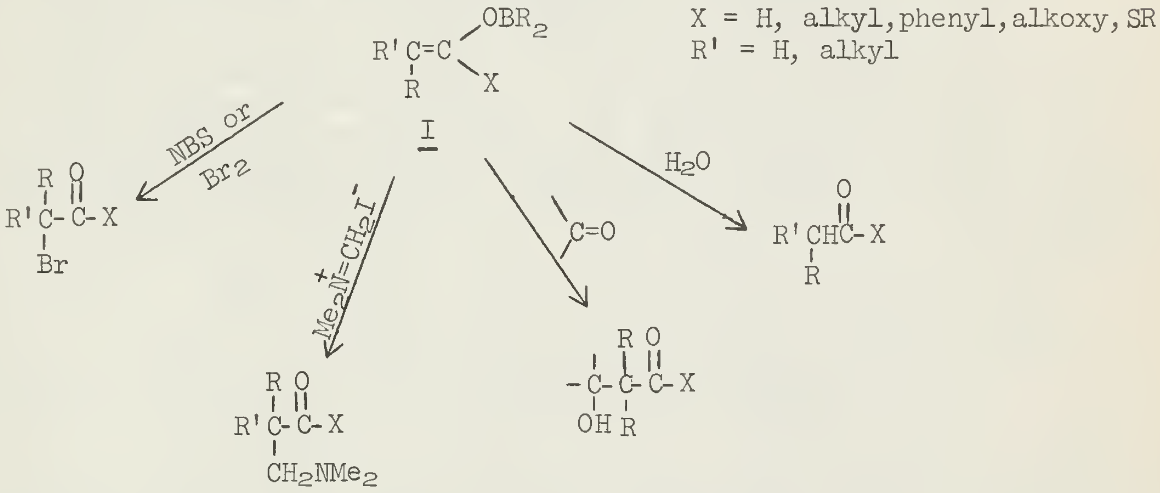
1. C. C. Hinckley, J. Amer. Chem. Soc., 91, 5160 (1969).
2. Reviews: a) I. Ya. Slonim and A. Kh. Bulia, Russ. Chem. Rev., 42, 904 (1973) b) J. K. M. Sanders and D. H. Williams, Nature (London), 240, 385 (1972); c) S. P. Sinha, J. Mol. Struct., 19, 387 (1973); d) B. C. Mayo, Chem. Soc. Rev., 2, 49 (1973); e) Nuclear Magnetic Resonance Shift Reagents, R. E. Sievers, Ed., Academic Press, N. Y. (1973); f) R. J. Convers, Organic Chemistr Seminar, U. of Illinois, 162, (1971).
3. M. D. McCleary, D. W. Lewis, D. L. Wernick and G. M. Whitesides, J. Amer. Chem. Soc., 96, 1038 (1974).
4. K. C. Yee and W. G. Bentrude, Tetrahedron Lett., 2775 (1971).
5. P. H. Mazzochi, H. J. Tamburin, and G. R. Miller, Tetrahedron Lett., 1819 (1971).
6. H. van Brederode and W. G. B. Huysmans, Tetrahedron Lett., 1695 (1971).
7. J. Reuben, J. Magn. Resonance, 11, 103 (1973).
8. L. F. Johnson, Tetrahedron Lett., 1703 (1971).
9. Z. W. Walkowshi, Tetrahedron Lett., 825 (1971).
10. D. C. Remy and W. A. Van Saun, Jr., Tetrahedron Lett., 2463 (1971).
11. J. W. Haan and L. J. M. Vande Ven, Tetrahedron Lett., 2703 (1971).
12. T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, Tetrahedron Lett., 1115, (1971).
13. M. R. Willcott and J. F. M. Oth, Tetrahedron Lett., 1579 (1971).
14. A. F. Cockerill and D. M. Rackham, Tetrahedron Lett., 5149 (1970).
15. R. R. Fraser and Y. Y. Wigfield, Chem. Commun., 1471 (1970).
16. W. Walter, R. F. Becker and J. Thiem, Tetrahedron Lett., 1971 (1971).
17. C. Beaute, Z. W. Wolkowski, J. P. Merda, and D. Lelandais, Tetrahedron Lett., 2473 (1971).
18. I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow, ref. 2e, p. 313.
19. G. L. Goe. J. Org. Chem., 38, 4285 (1973).
20. H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, J. Amer. Chem. Soc., 96, 1493 (1974).
21. G. J. Reich, G. R. Sullivan, and H. S. Mosher, Tetrahedron Lett., 1505 (1973).
22. K. Ajisaka, M. Kamisaku, and M. Kainosho, Chem. Soc. Japan, Chem. Lett., 857 (1972).

VINYLOXYBORANES AS SYNTHETIC INTERMEDIATES

Reported by Ikram M. Said   November 11, 1974

The use of organoboranes in the synthesis of various functional groups has been of great value to the organic chemists.[1] The existence of vinyloxyboranes 1 (or enol borinates as they are sometimes called) had been anticipated in the 1,4 addition reaction of organoboranes with α,β unsaturated carbonyl derivatives.[2] In 1971 Pasto and Wojtkowski[3] isolated and characterized several vinyloxyboranes from the reaction of organoboranes with certain diazocarbonyl compounds. Many workers have since then shown or inferred the intermediacy of vinyloxyboranes from various reactions, and have demonstrated that such intermediates are useful for the synthesis of various functional groups.

The vinyloxyboranes are usually generated *in situ*, and isolation of these intermediates is usually unnecessary. Some of the more common methods of generating vinyloxyboranes are the reaction of trialkylboranes with diazocarbonyl compounds[4-7] and α,β unsaturated carbonyl compounds.[8,9] Mukaiyama *et al.*, have generated vinyloxyboranes by the reaction of thioboronites with ketene[10] and substituted ketenes.[11] The reaction of trialkylboranes with readily enolizable ketones[12] has also been used, but not widely.



X = H, alkyl, phenyl, alkoxy, SR
R' = H, alkyl

The vinyloxyboranes derived from the reactions mentioned above can be hydrolysed to the corresponding aldehydes,[5] ketones[4,6] or esters.[7,13] Anhydrous conditions are usually required for other reactions of vinyloxyboranes (see reaction scheme). Condensation[10,11] with aldehydes and ketones would give rise to the corresponding β-hydroxy compounds; β-hydroxyalkanethionates can be obtained if a thioboronite instead of trialkylborane is used in the generation of the vinyloxyborane. In base catalyzed alkylation of ketones, various methods have been suggested to circumvent alkylation of both α-positions and polyalkylation. Alkylation of ketones (acyclic and cyclic) has been achieved via vinyloxyboranes but the approach is somewhat limited in scope.[14] The reaction of vinyloxyboranes with dimethyl(methylene)ammonium iodide[15] provides a simple route to Mannich bases without any problems associated with the usual Mannich condensation. The vinyloxyboranes can be halogenated with N-bromosuccinimide or N-chlorosuccinimide[16] to give the corresponding α-haloketones and esters; halogenation with bromine[9] has also been carried out.

The chemistry of vinyloxyboranes has been developed only in the last few years, but its synthetic utility has already been demonstrated. Further developments in this area will be of great value.

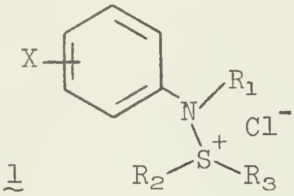
BIBLIOGRAPHY

1. H. C. Brown, "Boranes in Organic Chemistry", Cornell Univ. Press, Ithaca, (1972).
2. a) A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogic, and M. W. Rathke, J. Amer. Chem. Soc., 89, 5708 (1967); b) H. C. Brown, M. W. Rathke and G. W. Kabalba, ibid., 89, 5709 (1967).
3. D. J. Pasto and P. W. Wojtkowski, Tetrahedron Lett., 215 (1971).
4. J. Hooz and S. Linke, J. Amer. Chem. Soc., 90, 5936 (1968).
5. J. Hooz and G. F. Morrison, Can. J. Chem., 48, 868 (1970).
6. J. Hooz and D. M. Gunn, Chem. Commun., 139 (1969).
7. J. Hooz and S. Linke, J. Amer. Chem. Soc., 90, 6891 (1968).
8. a) H. C. Brown, G. W. Kabalba, A. Suzuki, S. Honma, A. Arase, and M. Itoh, ibid., 92, 710 (1970); b) H. C. Brown and M. M. Midland, Angew. Chem. Int. Edn., 11, 692 (1972).
9. A. Suzuki, N. Miyaura, M. Harada and M. Itoh, Chem. Lett., 1145 (1973).
10. T. Mukaiyama, K. Inomata and M. Muraki, Bull Chem. Soc. Japan, 46, 1807 (1973).
11. T. Mukaiyama, K. Inomata and T. Kawahara, Chem. Lett., 245 (1974).
12. W. Fenzl and R. Koster, Angew. Chem., 83, 807 (1971).
13. a) H. C. Brown, M. M. Midland and A. B. Levy, J. Amer. Chem. Soc., 94, 3662 (1972); b) J. Hooz, J. N. Bridson, J. G. Calzada, H. C. Brown, M. M. Midland, and A. B. Levy, J. Org. Chem., 38, 2574 (1973).
14. a) D. J. Pasto and P. J. Wojtkowski, ibid., 36, 1790 (1971); b) J. Hooz, D. M. Gunn and H. Kono, Can. J. Chem., 49, 2371 (1971).
15. J. Hooz and J. N. Bridson, J. Amer. Chem. Soc., 95, 602 (1973).
16. J. Hooz and J. N. Bridson, Can. J. Chem., 50, 2387 (1972).

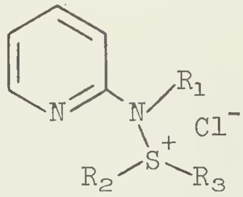
AZASULFONIUM SALTS: INTERMEDIATES FOR SYNTHESIS

Reported by William F. Pfohl November 14, 1974

The importance of azasulfonium salts, 1 and 2, as reaction intermediates in organic synthesis has become apparent over the past few years.



1



2

Depending upon the nature of R_1, R_2, R_3, and X, 1 can be utilized as an intermediate for the synthesis of ortho-substituted anilines,[1-7,10] indoles,[2,8-10] oxindoles,[2,10-12] and carbazoles.[8] Many of these compounds are important to natural product chemistry. Azasulfonium salts, 2, derived from 2-aminopyridine are intermediates for the synthesis of azaindoles and substituted pyridines.[13]

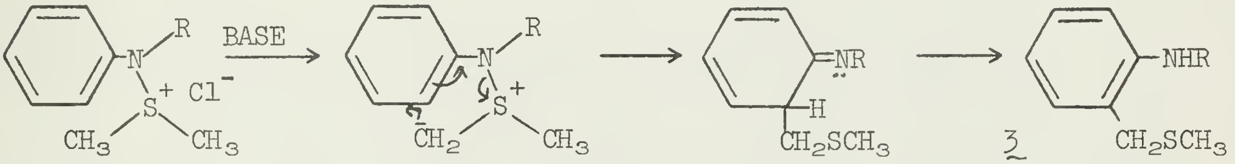
Synthesis:

Johnson and co-workers[3] prepared N-methylanilinophenylmethyl sulfonium tetrafluoroborate in 70% yield from the reaction of phenylmethylsulfide and 1-chlorobenzotriazole followed by reaction with N-methylaniline and silver fluoroborate. A simpler and more convenient method for the preparation of azasulfonium salts, 1, involves the reaction of an N-chloroaniline with a dialkyl sulfide at low temperature.[4,5,6] The scope of the reaction has been expanded to include various substituted N-chloroanilines as well as β-keto sulfides,[2,8,9] α-formyl sulfides and their derivatives,[9] α-carboalkoxy sulfides,[2,11,12] arylalkyl sulfides,[1,7] and cyclic sulfides.[2,5,6] A severe limitation to this method arises when the N-chloroaniline is substituted with a para-methoxyl group. In this case, yields were very low. This was rationalized by the observation that solvolysis of N-chloroanilines in buffered ethanol into nitrenum ions and chloride ions occurs with a $\rho = -6.35$[14,15] suggesting that a strong cation stabilizing group in the para position leads to a very unstable N-chloroaniline. Anilines and substituted anilines react readily with halogen-sulfide complexes at low temperature[2,10] to yield azasulfonium salts directly. Using this method, azasulfonium salts 1 ($X=p\text{-}OCH_3$) can be prepared in good yield. Halogen-sulfide complexes have been discussed in terms of halosulfonium halide salts as well as sulfuranes.[16-19] Gassman and Huang[13] prepared azasulfonium salts, 2, from the reaction of N-chloro-2-aminopyridine and the appropriate sulfide.

Reactions:

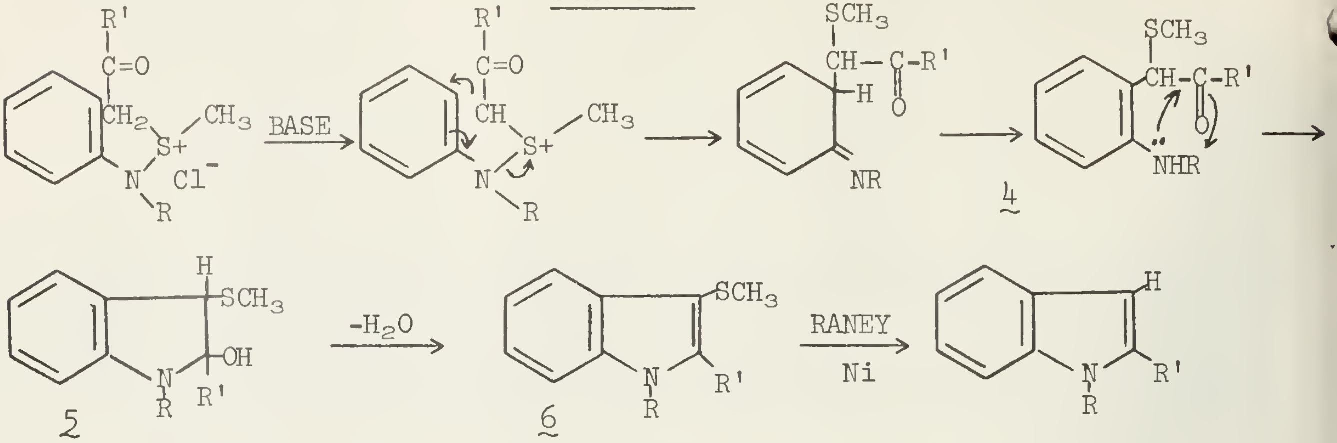
Azasulfonium salts, 1, derived from an aniline and dimethyl sulfide react with base to form an ylide which undergoes a Sommelet-Hauser type rearrangement[21,22] followed by rearomatization exclusively to the ortho-thiomethoxymethyl aniline (3).[1-7,10] Compound 3 may then be desulfurized with Raney nickel or $LiAlH_4$ yielding the corresponding ortho-methyl aniline. (Scheme I).

Scheme I



Cyclic sulfides may be utilized to obtain ortho-n-alkylanilines[2,5,6] while use of benzylphenylsulfides allows for the synthesis of ortho-benzylanilines[1] which are important intermediates for the synthesis of fluorenes. Selective ortho formylation of aromatic amines has also been achieved[7] in a similar manner. The use of β-keto sulfides[2,8,9] and α-formyl sulfides[9] lead to azasulfonium salts, 1, which upon treatment with base yields 4 (Scheme II). Intramolecular addition of the free amine to the carbonyl of 4 leads to an α-aminoalcohol 5 which dehydrates to yield an indole, 6. That 4 is actually an intermediate is supported by the isolation of the ketal of 4 when the ketal of the β-keto sulfide was used.[9]

Scheme II



Base treatment of 1 derived from α-carboalkoxy sulfides[2,11,12] leads to intermediates 4 (R'=OR) which upon treatment with acid yield 3-thiomethoxy oxindoles. Azasulfonium salts 2 undergo analogous reactions[13] to give good yield of ortho substituted heterocyclic amines as well as azaindoles and 2-substituted-7-azaindoles.

Variation in the substitution of the anilines and sulfides used in preparing the azasulfonium salts allows for the synthesis of a wide variety of compounds. Since many naturally occurring indoles are substituted in the 2-and 3-positions the synthesis of 2,3-disubstituted indoles[8] by the above methods is of particular importance.

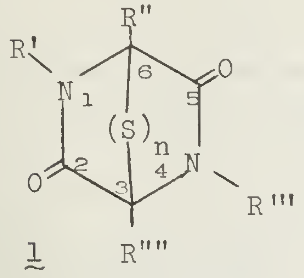
The use of azasulfonium salts offers many advantages over older methods of synthesis of ortho-substituted anilines, indoles, and oxindoles. Starting materials are inexpensive and readily available[9] which for indoles is not the case with the Fischer synthesis.[20] Azasulfonium salts have much to offer as effective intermediates for organic synthesis.

Bibliography

1. P.G. Gassman and H.R. Drewes, J. Chem. Soc. Chem. Commun., 488 (1973).
2. P.G. Gassman, T.J. van Bergen and G. Gruetzmacher, J. Amer. Chem. Soc., 95, 6508 (1973).
3. C.R. Johnson, C.C. Bacon and W.D. Kingsbury, Tetrahedron Lett., 501 (1972).
4. P.G. Gassman and G. Gruetzmacher, J. Amer. Chem. Soc., 95, 588 (1973).
5. P.G. Gassman, G. Gruetzmacher and R.H. Smith, Tetrahedron Lett., 497 (1972).
6. P.G. Gassman and G. Gruetzmacher, J. Amer. Chem. Soc., 96, 5487 (1974).
7. P.G. Gassman and H.R. Drewes, ibid., 96, 3002 (1974).
8. P.G. Gassman, D. Gilbert and T.J. van Bergen, J. Chem. Soc. Chem. Comm., 201 (1974).
9. P.G. Gassman, T.J. van Bergen, D. Gilbert and B.W. Cue, Jr., J. Amer. Chem. Soc., 96, 5495 (1974).
10. P.G. Gassman, G. Gruetzmacher and T.J. van Bergen, ibid., 96, 5512 (1974).
11. P.G. Gassman and T.J. van Bergen, ibid., 95, 2718 (1973).
12. P.G. Gassman and T.J. van Bergen, ibid., 96, 5508 (1974).
13. P.G. Gassman and C.T. Huang, ibid., 95, 4453 (1973).
14. P.G. Gassman, G.A. Campbell and R.C. Frederick, ibid., 94, 3884 (1972).
15. P.G. Gassman and G.A. Campbell, ibid., 94, 3891 (1972).
16. I.C. Paul, J.C. Martin and E.F. Perozzi, ibid., 93, 6674 (1971).
17. N. Furukawa, T. Inove, T. Aida and S. Oae, Chem. Commun., 212 (1973).
18. G.E. Wilson, Jr., and R. Albert, J. Org. Chem., 38, 2160 (1973).
19. E.J. Corey and C.U. Kim, J. Amer. Chem. Soc., 94, 7586 (1972).
20. B. Robinson, Chem. Rev., 69, 227 (1969).
21. G.C. Jones and C.R. Hauser, J. Org. Chem., 27, 3572 (1962).
22. C.R. Hauser and S.W. Kantor, J. Amer. Chem. Soc., 73, 1437, 4122 (1951).

SYNTHETIC APPROACHES TO EPIPOLYTHIODIKETOPIPERAZINES

Reported by Arthur Haber November 18, 1974



1

Naturally occurring epipolythiodiketopiperazines (TDKP's), 1, are a subclass of diketopiperazine-derived fungal metabolites,[1,2] which are of great pharmacological and chemical interest. Members of this subclass include gliotoxin,[3,4] sporidesmins A-G,[5-8] the aranotins,[9,10] verticillin A,[11] chaetocin,[12] chetomin,[13] and possibly other sulfur containing natural products whose structures are as yet undetermined.[14,15] The biological properties of these compounds have been reviewed.[12,14,16,17] The structures of these TDKP's have been determined by chemical and physical methods, x-ray analyses, and circular dichroism studies, and conformational analyses of some di-, tri-, and tetra-sulfides have been briefly discussed.[2-12,18] Biosynthetic studies on gliotoxin[2,19] the aranotins[10,20] and sporidesmin A,[2,30] have been published.

Prior to 1970 the only synthetic approach to the TDKP system--aside from chemical interconversions of some sporidesmins[5,16]--was that of Trown.[21] Starting with sacrosine anhydride, he was able to obtain 3,6-epidithio-1,4-dimethyl-2,5-diketopiperazine. Two similar approaches to a simple TDKP system have also been described.[22,23]

An approach to TDKP's involving the addition of sulfur to the analogous DKP's has been described for the sporidesmins,[24] and a synthesis of DKP's analogous to gliotoxin has also been described.[25] Pojer and Rae[26] have synthesized 2-benzamido-2-mercaptopropanoic acid and then formed the dimer, presumably with the intention of forming a TDKP. Witkop and co-workers have attempted to synthesize analogs of gliotoxin by initially constructing the disulfide bridge on substituted indoles by reaction of sulfur nucleophiles followed by ring closure to the TDKP.[27] Schmidt and co-workers have expended considerable effort toward the development of methods for the introduction of sulfur functions and alkyl groups into a DKP ring.[28]

A new, general method for the synthesis of TDKP's, which has been applied to the total syntheses of dehydrogliotoxin, sporidesmin A, and sporidesmin B, has been developed by Kishi and co-workers.[29] This method involves formation of a protected TDKP by the reaction of p-anisaldehyde and cis- or trans-3,6-dithiol-1,4-dimethyl-2,5-diketopeiperazine. Conversion to the TDKP is accomplished by sequential treatment with m-chloroperbenzoic acid and boron trifluoride etherate.

BIBLIOGRAPHY

1. R. L. Cundall, University of Illinois Seminar Abstract, December 7, 1970.
2. W. B. Turner, "Fungal Metabolites," Academic Press, New York, New York, 1971, p 320.
3. J. R. Johnson, "The Structure of Gliotoxin," in "The Roger Adams Symposium," John Wiley & Sons, Inc., New York, New York, 1955, p 60.
4. J. R. Johnson, M. R. Bell, B. S. Wildi, and R. B. Woodward, J. Amer. Chem. Soc., 80, 1001 (1958).
5. Sporidesmins. Parts I-XII. Part XII: E. Francis, R. Rahman, S. Safe, and A. Taylor, J. Chem. Soc., Perkin I, 470 (1972) and references cited therein.
6. R. Rahman and A. Taylor, Chem. Commun., 1032 (1967).
7. D. Brewer, R. Rahman, S. Safe, and A. Taylor, ibid., 1571 (1968).
8. R. Hodges and J. S. Shannon, Aust. J. Chem., 19, 1059 (1966).

9. R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, J. Amer. Chem. Soc., 90, 2980 (1968).
10. N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huchstep, Tetrahedron Lett., 4467 (1968).
11. H. Minato, M. Matsumoto, and T. Katayama, Chem. Commun., 44, (1971).
12. D. Hauser, H. P. Weber, and H. P. Sigg, Helv. Chim. Acta, 53, 1061 (1970).
13. S. Safe and A. Taylor, J. Chem. Soc., Perkin I, 472 (1972).
14. A. Taylor, "The Chemistry and Biochemistry of Sporidesmins and Other 2,5-Epidithia-3,6-dioxopiperazines," in "Biochemistry of Some Foodborne Microbial Toxins," R. I. Mateles and G. N. Wogan, eds., The M. I. T. Press, Massachusetts Institute of Technology, Cambridge, Mass., 1967, p 69 and references cited therein.
15. A. Kato, T. Saeki, S. Sezuki, K. Ando, G. Tamura, and K. Arima, J. Antibiot 22, 322 (1969).
16. A. Taylor, "The Toxicology of Sporidesmins and Other Epipolythiadioxopiperazines," in "Microbial Toxins," Vol. VII, S. Kadis, A. Ciegler, and S. Ajl, eds., Academic Press, New York, New York, 1971, p 337 and reference cited therein.
17. P. A. Miller, K. P. Milstrey, and P. W. Trown, Science, 159, 431 (1968).
18. M. Prizybylska, E. M. Gopalakrishna, A. Taylor, and S. Safe, Chem. Commun., 554 (1973); R. Nagarajan and R. W. Woody, J. Amer. Chem. Soc., 95, 7212 (1973) and references cited therein; R. Rahman, S. Safe, and A. Taylor, Quart. Rev. (London), 24, 226 (1970).
19. J. D. Bu'Lock and A. P. Ryles, Chem. Commun., 1404 (1970) and 100 (1972); and M. S. Ali, J. S. Shannon, and A. Taylor, J. Chem. Soc., C, 2044 (1968).
20. N. Neuss, et al., Antimicrobiol. Agents Chemother., 213 (1968) and D. R. Brannon, J. A. Mabe, B. B. Malloy, and W. A. Day, Biochem. Biophys. Res. Commun., 43, 588 (1971).
21. P. W. Trown, ibid., 33, 402 (1968).
22. S. G. Svokos and R. B. Angier, Chem. Abstr., 74, 53845p (1971).
23. T. Hino and T. Sato, Tetrahedron Lett., 3127 (1971).
24. M. Ohno, T. P. Spande, and B. Witkop, J. Amer. Chem. Soc., 90, 6521 (1968).
25. N. T. Modi, S. R. Ahmed, A. R. Kidwai, and J. R. Johnson, J. Org. Chem., 35, 2228 (1970).
26. P. M. Pojer and I. D. Rae, Tetrahedron Lett., 3077 (1971) and Aust. J. Chem., 25, 1737 (1972).
27. H. C. J. Ottenheym, T. P. Spande, and B. Witkop, J. Amer. Chem. Soc., 95, 1989 (1973).
28. H. Poisel and U. Schmidt, Angew. Chem. Int. Ed. Engl., 10, 130 (1971); Chem. Ber., 104, 1714 (1971); ibid., 105, 625 (1972); E. Öhler, F. Tataruch and U. Schmidt, ibid., 105, 635 (1972); E. Öhler, P. Tataruch and U. Schmid ibid., 105, 3658 (1972); ibid., 106, 165 (1973), and ibid., 106, 396 (1973).
29. Y. Kishi, T. Fukuyama, and S. Nakatsuka, J. Amer. Chem. Soc., 95, 6490 (1973) and ibid., 95, 6492 (1973); Y. Kishi, S. Nakatsuka, T. Fukuyama, and M. Havel, ibid., 95, 6493 (1973), and S. Nakatsuka, T. Fukuyama, and Y. Kish Tetrahedron Lett., 1549 (1974).
30. G. W. Kirby and M. J. Varley, Chem. Commun., 833 (1974).

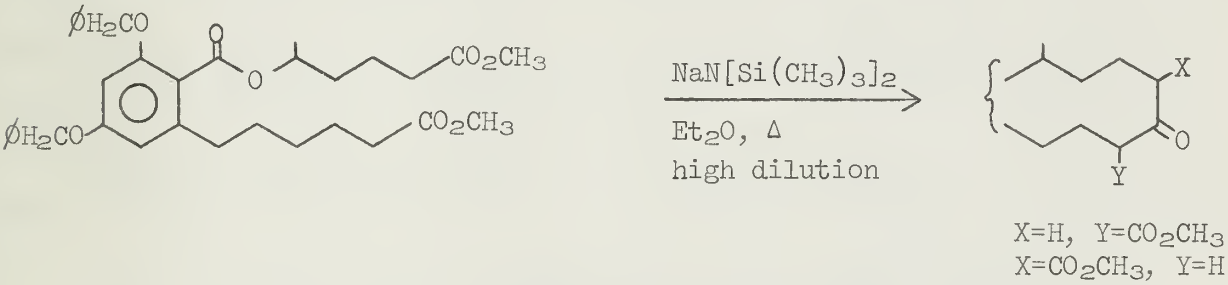
SOME APPROACHES TO THE SYNTHESIS OF MACROCYCLIC COMPOUNDS

Reported by Marvin Reich November 25, 1974

The study of large ring compounds has become increasingly important in recent years. Theoretical chemists have examined such systems in order to learn more about transannular effects, strain, aromaticity, conformation, and reactivity. Macrocyclic compounds constitute a significant class of natural products, many of which have interesting biological activity.[1] The synthesis of these materials presents some unique problems for the organic chemist.[2] Practical solutions to these problems will be discussed, with special attention given to those procedures applicable to natural product synthesis. The most useful reactions will be grouped into two types: cyclization and scission of bonds in polycyclic precursors.

CYCLIZATION REACTIONS

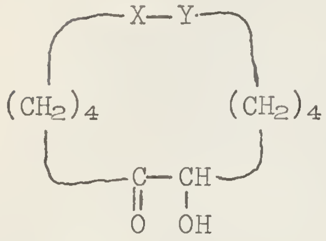
Bifunctional molecules can undergo either polymerization or ring formation, depending on their structure or reaction conditions. In all cases other than those of 5- and 6-membered rings, the intermolecular reaction is thermodynamically favored.[3] The difficulties associated with the preparation of macrocyclic compounds by ring closure are due to the low probability that the ends of a long chain will meet. The cyclization reaction can be made to predominate by use of high dilution or by various structural factors which make more probable those chain conformations leading to intramolecular reaction. Among the earliest reactions used for the preparation of large rings were the Dieckmann[4a], Thorpe-Ziegler[4a,b], and acyloin.[4c] The Dieckmann reaction was first applied to large rings in the 1940's. Seven-and 8-membered rings have been made in fair yields while the analogous C_9-C_{12} cyclic ketones were obtained in very low yields; cyclic dimer formation was common.[4a] The widely held belief that the Dieckmann was only applicable to 5-, 6-, and 7-membered rings was discredited by Leonard and Schimelpfenig.[5] Using high dilution conditions with potassium t-butoxide in xylene, they obtained 24-48% yields of C_{13}, C_{14}, and C_{15} cycloalkanones. In studies directed toward the total synthesis of (R,S)-zearalanone, Hurd and Shah[6] examined the formation of 2,4-dibenzylethers of carbomethoxyzearalanone from an open-chain diester by slow addition techniques. The combined yield of isomeric products (77%) was quite high for this type of reaction.



The Thorpe condensation of nitriles is analogous to the Dieckmann and was first applied by Ziegler in the 1930's to the cyclization of aliphatic α,ω-dinitriles. The condensing agent is most commonly an alkali metal salt of an N-alkylaniline and the reaction is carried out under high dilution conditions in ether. Hydrolysis of the primary reaction product (an enaminonitrile) gives a cyclic ketone in very high yield for rings with five to eight carbons, poor yields for 9- to 12-membered rings, and yields of about 70% for larger rings.[4a,b.]

The acyloin has been the most commonly used reaction for the preparation of simple macrocyclic ketones. The procedure consists of heating an α,ω-diester in aromatic solvents with finely dispersed sodium. High dilution conditions have been used for medium-sized rings. Yields of cyclic acyloins generally increase as the ring size gets larger with a minimum (40-70%) at C_9

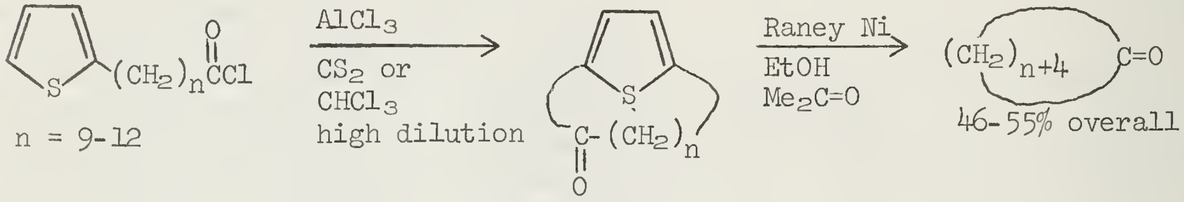
to C_{12}. It has long been the most practical route to medium-sized rings. The mechanism is believed to be free radical as the two ends of the open-chain precursor are held on the surface of the sodium. A variety of functional groups can be tolerated:



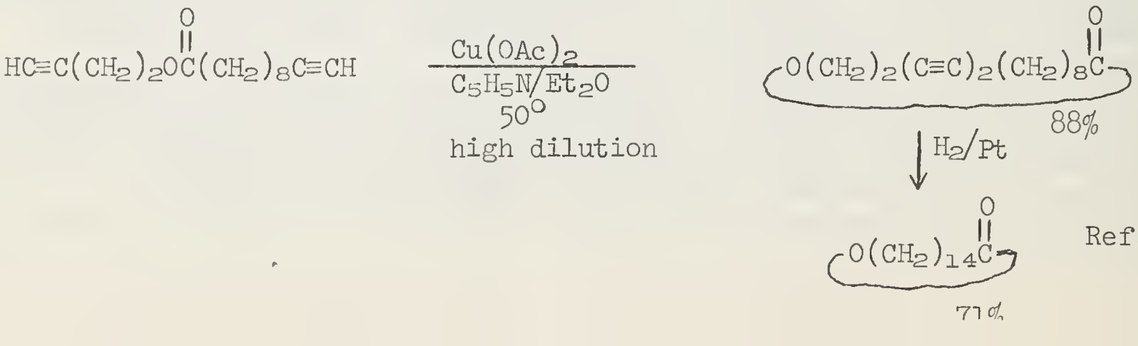
X—Y	Yield	Ref.
C≡C	73%	7
trans CH=CH	51%	7
cis CH=CH	78%	7
$CH_3N<$	64%	8

The musk ketones civetone, exaltone, and muscone are important to the perfume industry and provided the incentive for the first applications of the acyloin in the synthesis of macrocyclic ketones.[9]

Russian workers have devised novel syntheses of a variety of cyclic compounds[10] based upon the unique properties of the thiophene ring. Their method exemplifies a widely held belief, first proposed by Baker[11] - if part of the molecule to be cyclized is constrained in a rigid structure (ring, multiple bond), cyclization will be favored due to a decrease in the number of "non-productive conformations" and transannular interactions. Finely divided aluminum chloride was used and it was believed that reaction took place on the surface of these particles.[12] Since the α-position of thiophene is more reactive than the β-position, acylation will go here preferentially unless this would lead to an unfavorable ring size fused to the thiophene.[13] Cyclization could also be effected by intramolecular alkylation of an acetoacetic ester[14] or by acyloin reaction on a fully substituted thiophene.[15] In all cases, desulfurization was done with Raney nickel. The cyclized thiophene could be functionalized by Friedel Crafts alkylation or acylation.[16] Macrocyclic ketolactones, models for the macrolide antibiotics, could be made by incorporating an ester into one of the substituent chains.[17]

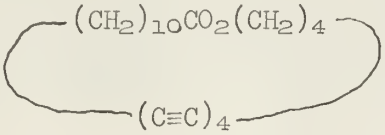


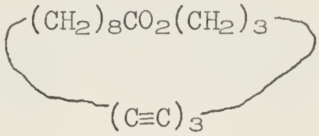
The oxidative coupling of α,ω-diacetylenes (Glaser reaction) to give macrocyclic compounds has been used extensively by Sondheimer[18] in his investigations of annulenes. Other groups have conducted the reaction under conditions of high dilution. The detailed mechanism of the coupling reaction is unknown.[19] A commercially important macrolide, exaltolide, was made by this procedure:



Ref. 20

More concentrated solutions led to cyclic oligomers. Tri- and tetra-acetylenic compounds were obtained in model reactions for the synthesis of polyene antibiotics:

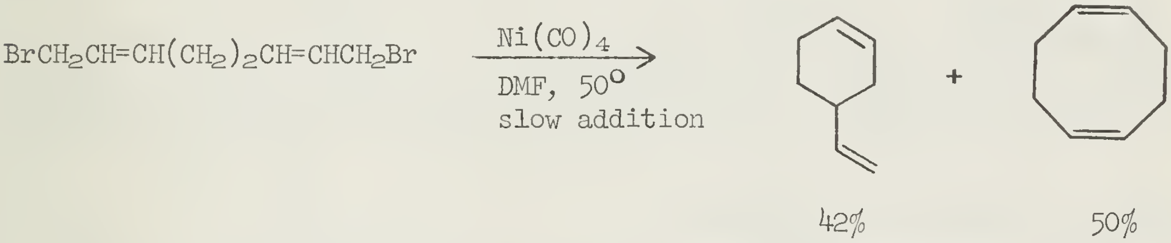


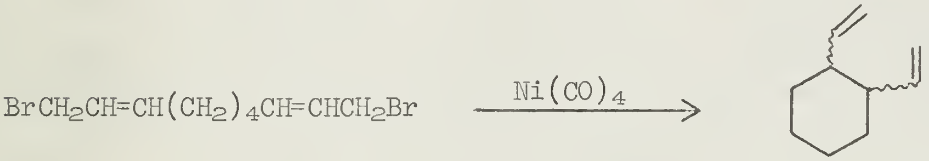


Ref. 21

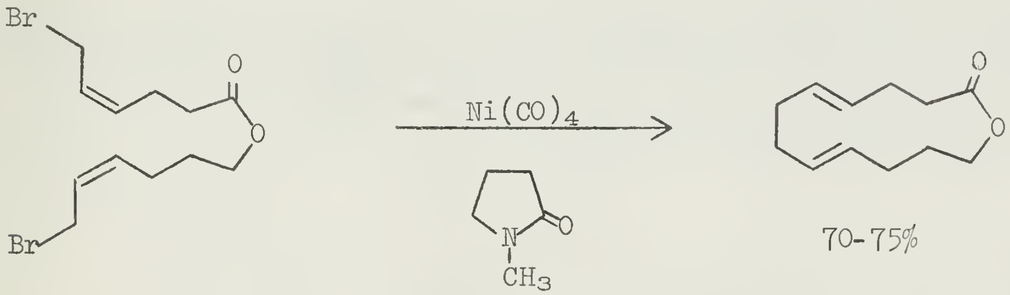
Hydrogenation over Lindlar catalyst/quinoline gave complex mixtures from which the all cis polyene could be isolated; photolysis yielded a new product presumed to be the all trans compound.

Corey has made an important contribution to synthetic methodology in this area by developing the nickel tetracarbonyl mediated coupling of allylic dibromides to produce macrocyclic 1,5-dienes. Previous work by Corey[22] and others[23] had demonstrated that simple allylic halides could be coupled by use of nickel tetracarbonyl. Corey and Wat[24] showed that long chain allylic dibromides: $BrCH_2CH{=}CH(CH_2)_nCH{=}CHCH_2Br$, n=2, 4, 6, 8 and 12 could be efficiently cyclized by slow addition to nickel tetracarbonyl. Either pure cis,cis or trans,trans dienes (n=6, 8, and 12) gave 60-85% yields of cyclic t,t-1,5 dienes. Shorter precursors tended to form 6-membered rings where possible:

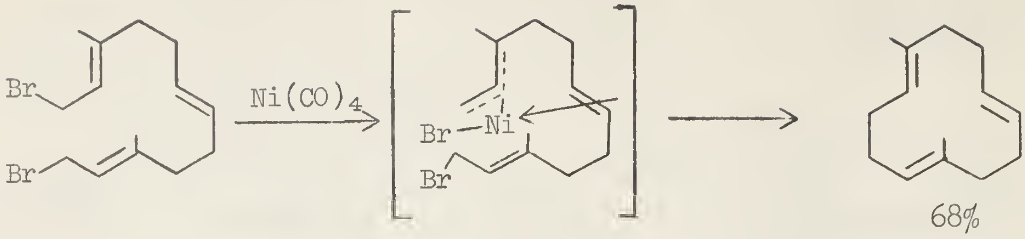




Corey and Kirst[25] later applied the reaction to a 13-membered macrolide:

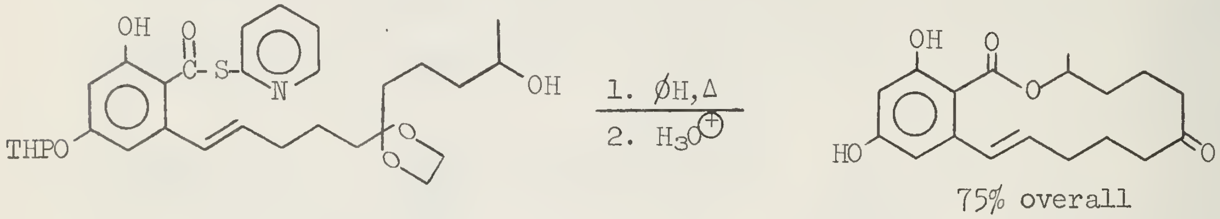


The exact mode of carbon-carbon bond formation is not known but is believed to be radical-like coupling within a nickel complex.[26] A π-allylnickel (I) bromide is an important intermediate in the reaction; participation of bis-π-allylnickel (0) complexes may also be necessary for coupling. The reaction requires carbon monoxide and a polar coordinating solvent, probably to activate the allyl ligand. The nickel atom may also exert a template effect in some cases:[27]



Cyclization of the analogous compound without an internal double bond gave a 4% yield of product. This method was a key step in the synthesis of the isoprenoid natural products humulene[28] and cembrene.[29]

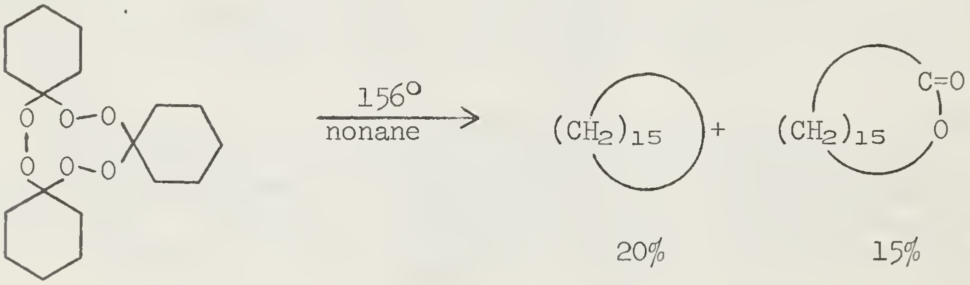
Corey has recently described a new method of macrolide formation[30] in which the carboxyl group of an ω-hydroxyacid is activated as the 2-pyridine thiolester. A series of ω-hydroxyacids, $HO(CH_2)_nCO_2H$ ($n = 5, 7, 10, 11, 12, 14$), was cyclized by slow addition of their pyridine thiolesters to refluxing xylene. Good yields of monomeric lactones were obtained except for 9- and 12-membered rings where cyclic dimers were the major products. An excellent yield of the naturally occurring macrolide zearalenone was obtained by this method.



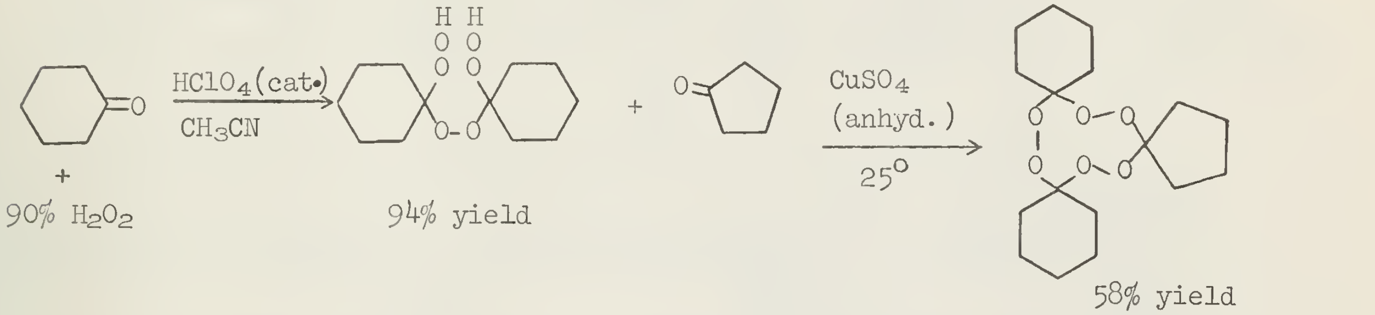
CLEAVAGE OF POLYCYCLIC PRECURSORS

When a many-membered ring is formed directly from a linear molecule the reaction is usually carried out in very dilute solution with slow, controlled addition of reagents. This may limit the practical application of the methods. This disadvantage does not apply to syntheses involving a transannular bond. Here, the macrocycle is formed from a polycyclic system containing more readily accessible 3- to 7-membered rings. Cleavage of the transannular bond to form the macrocycle may also create new functionality at the point of scission which can enable further transformations to be carried out.

Story's peroxide fragmentation reaction is a general method for the preparation of macrocyclic compounds and has been applied to carbocyclic systems from C_8 through C_{33}.[2c] The reaction consists of the photolytic or thermal decomposition of a di- or tricycloalkylidene peroxide as shown below for tricyclohexylidene peroxide:

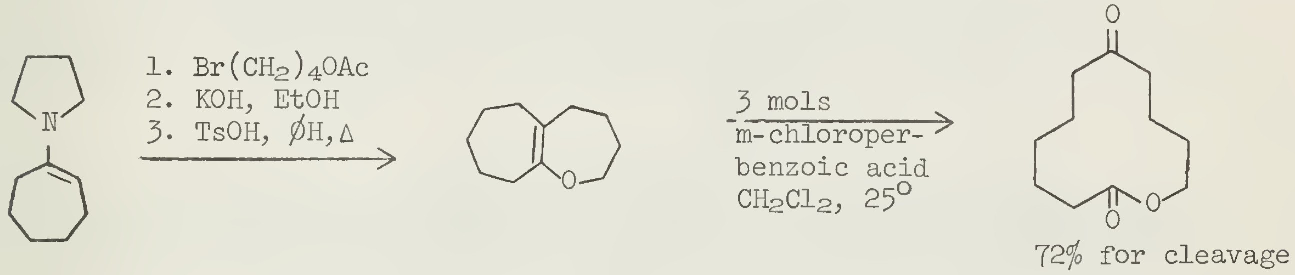


The solvent is later removed by short path distillation and the residual liquid is distilled through a spinning band column. Yields of cyclic hydrocarbons (C_{12}-C_{15}, C_{18}, C_{23}) from tricycloalkylidene precursors vary from 15-30% with the accompanying lactones present in 15-25% yields.[2c] Symmetrical cycloalkylidene peroxides can sometimes be prepared by controlled reaction of a cyclic ketone with hydrogen peroxide in the presence of a mineral acid catalyst.[2c] A better procedure is to make various 1,1'-dihydroperoxy peroxides under controlled conditions and then condense these with cycloalkanones.[2c, 31]



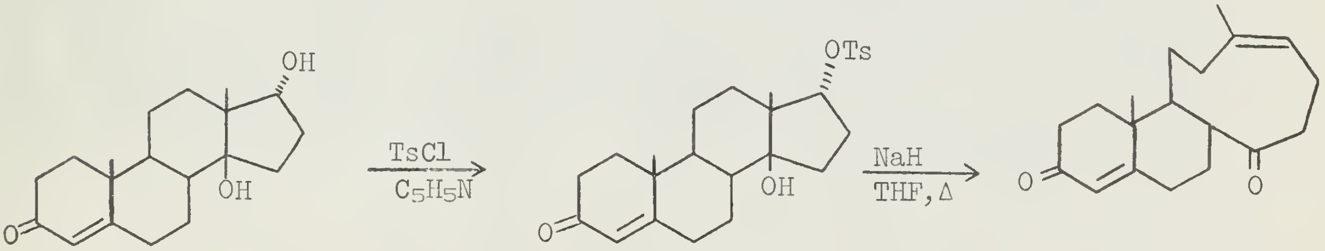
Details of the decomposition of dicycloalkylidene peroxides have not been published but by analogy to other free radical reactions the first step is presumed to be homolysis of the O-O bond. This would be followed by β-scission, rapid cage recombination of the alkyl radicals, and decarboxylation of the resulting diacyl peroxide.[32] Lactone would be formed by carboxy inversion followed by rearrangement with loss of carbon dioxide.

Oxidative cleavage of certain bicyclic enol ethers has provided a route to various macrocyclic compounds, among them the parent ring systems of two antibiotics methmycin[33] and erythromycin.[34] 7-Ketoundecanolide, the structural system of the methmycin antibiotics was made in the following manner.[33]

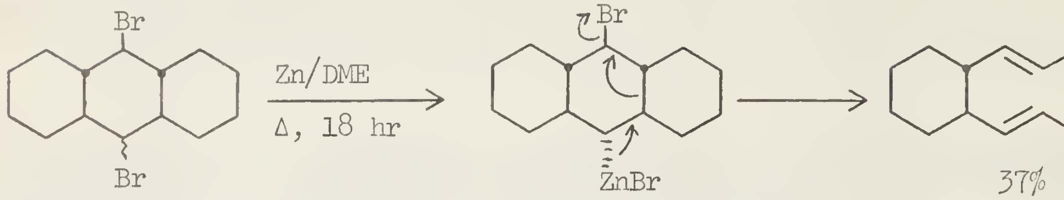


The bicyclic precursor can also be obtained by addition of acrylic esters to enamines[33] or by alkylation of a cyclic β-ketoester with an ω-bromoacetate.[34] A mechanism involving epoxidation and ring opening with addition of the peracid followed by transannular cleavage has been proposed.[33, 35] Cleavage of bicyclic enol ethers or enamines can also be effected with butyl nitrite in aqueous ethanol to give the oximino macrolide which can then be hydrolyzed to a ketolactone.[36]

The base induced cleavage of monosulfonates of 1,3-glycols is an important route to medium-sized rings. The utility of this reaction was first demonstrated by Wharton.[37] A novel application has been the formation of a 13,14-secosteroid:[38]

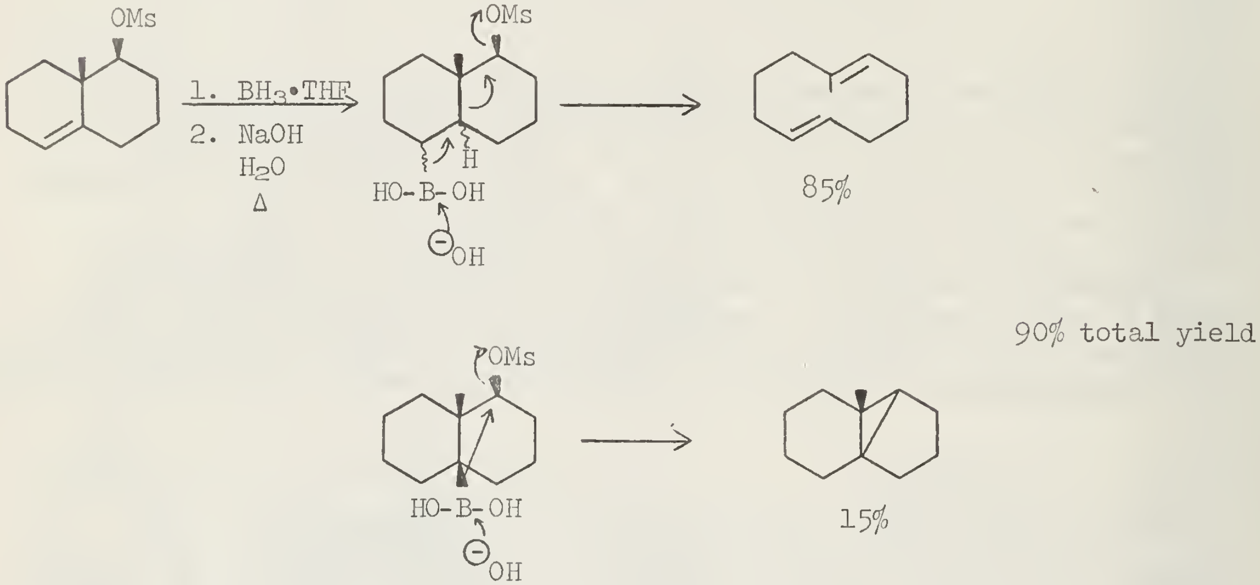


The stereochemical requirements for this reaction have been determined by Wharton who examined the fragmentation of various decalin derivatives[39]; related reactions have been discussed by Grob.[39b] Variations on this scheme have been transannular debromination[40] and cleavage at a bridging carbon atom.[41]

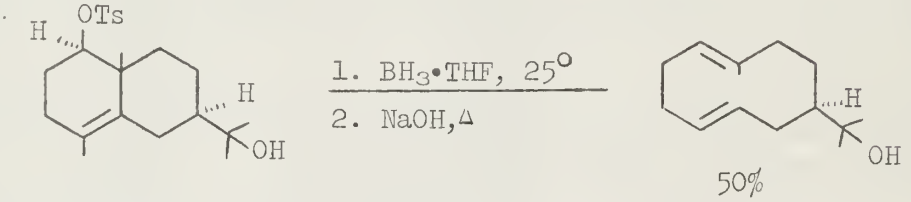


Ref. 40

An important modification, the boronate fragmentation, was introduced by Marshall[42]:



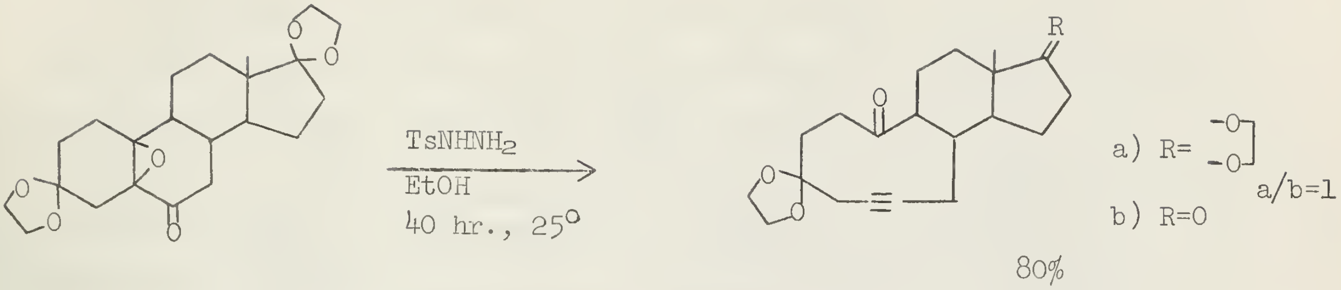
The biogenetically important terpene, hedycaryol, has been synthesized from a fully functionalized precursor by this reaction:



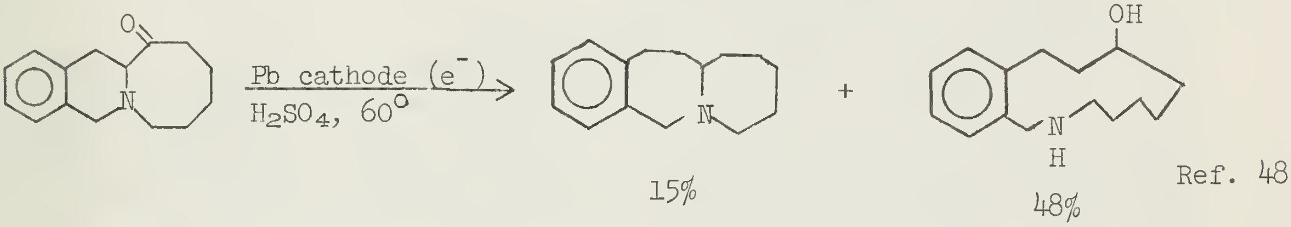
Ref. 43

A key step in Corey's synthesis of both caryophyllene and isocaryophyllene was the cleavage of a fused 5,6-system to generate a 9-membered ring.[44]

Eschenmoser has developed a general method for the preparation of acetylenic carbonyl compounds by fragmenting α,β-epoxyketones.[45] Cleavage is induced by treating the epoxyketone with tosylhydrazine in the presence of dilute acid or base, by reacting the corresponding oximino epoxide with hydroxylamine O-sulfonic acid and base, or by heating the imide formed from the epoxyketone and N-aminoaziridine. Exaltone and muscone have been made by this procedure.[46]



Leonard and co-workers have synthesized some medium ring heterocycles by electrolytic cleavage of bicyclic precursors.[47,48] The mechanism involves



electron-induced C_α-N cleavage followed by intramolecular attack of nitrogen on carbonyl carbon or further reduction.[49]

Several important natural products or related compounds have been synthesized by reactions not discussed above: (+)-di-O-methylcurvularin,[50] zearalenone,[51] dideoxyzearalane,[52] pyrenophorin,[53] and 5-acetoxy-9-oxotridecanolactone.[54]

BIBLIOGRAPHY

1. Macrolide antibiotics: D. Gottlieb and P. D. Shaw, "Antibiotics," Vol. 1, Springer Verlag, New York, 1967. Ansamycins: K. L. Rinehart, Jr., Accounts Chem. Res., 5, 57, (1972). Anti-tumor: S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Haltiwanger and R. F. Bryan, J. Amer. Chem. Soc., 94, 1354, (1972). Uterotrophic: W. H. Urry, H. L. Wehrmeister, E. B. Hodge and P. H. Hidy, Tetrahedron Lett., 3109, (1966).
2. For reviews see: a) K. Ziegler in Houben-Weyl, "Methoden der Organischen Chemie," Vol. 4, Pt. 2, (4 ed.), Georg Thieme Verlag, Stuttgart, 1955, P. 729; b) L. I. Belenkii, Russ. Chem. Rev., 33, 551, (1964); c) P. R. Story and P. Busch, Adv. Org. Chem.. 8, 67, (1972).
3. P. J. Flory, Chem. Rev., 39, 137, (1946).
4. a) J. P. Schaeffer and J. J. Bloomfield, Org. React., 15, 1, (1967); b) E. C. Taylor and A. McKillop, Adv. Org. Chem., 7, 1, (1970); c) S. M. Mc Elvain, Org. React., 4, 256, (1948). K. T. Finley, Chem. Rev., 64, 573, (1964).
5. N. J. Leonard and C. W. Schimelpfenig, Jr., J. Org. Chem. 23, 1708, (1958).
6. R. N. Hurd and D. H. Shah, J. Org. Chem., 38, 390, (1973). R. N. Hurd and D. H. Shah, J. Med. Chem., 16, 543, (1973).
7. D. J. Cram and N. L. Allinger, J. Amer. Chem. Soc., 78, 2518, (1956). D. J. Cram and L. K. Gastin, J. Amer. Chem. Soc., 82, 6386, (1960).
8. N. J. Leonard, R. C. Fox and M. Oki, J. Amer. Chem. Soc., 76, 5708 (1954).
9. M. Stoll and A. Rouvé, Helv. Chim. Acta, 30, 1822, (1947). M. Stoll, J. Hulstkamp and A. Rouvé, Helv. Chim. Acta, 31, 543, (1948). M. Stoll and A. Commarmont, Helv. Chim. Acta, 31, 554, (1948).

10. Ya. L. Goldfarb, S. Z. Taits and L. I. Belenkii, Tetrahedron, 19, 1851 (1963).
11. W. Baker, J. F. W. McOmie and W. D. Ollis, J. Chem. Soc., 200, (1951).
12. L. I. Belenkii, S. Z. Taits and Ya. L. Goldfarb, Proc. Acad. Sci., USSR, 139, 838, (1961).
13. Ya. L. Goldfarb, S. Z. Taits and L. I. Belenkii, Bull. Acad. Sci., USSR, 1320, (1973).
14. Ya. L. Goldfarb, S. Z. Taits and V. N. Bulgakova, Bull. Acad. Sci., USSR, 1181, (1963).
15. S. Z. Taits and Ya. L. Goldfarb, Bull. Acad. Sci., USSR, 1173, (1963).
16. Ya. L. Goldfarb, S. Z. Taits, T. S. Chirkova and L. I. Belenkii, Bull. Acad. Sci., USSR, 1948, (1964).
17. S. Z. Taits, F. D. Alashev and Ya. L. Goldfarb, Bull. Acad. Sci., USSR, 550, (1968).
18. F. Sondheimer, Chimia, 28, 163, (1974), and earlier papers.
19. G. Eglinton and W. McCrae, Adv. Org. Chem., 4, 225 (1963). T. F. Rutledge, "Acetylenic Compounds; Preparation and Substitution Reactions," Reinhold Book Co., New York, (1968).
20. W. McCrae, Tetrahedron, 20, 1773 (1964).
21. L. D. Bergelson and Yu. G. Molotkovskii, Bull. Acad. Sci., USSR, 94, (1963).
22. E. J. Corey and M. F. Semmelhack, Tetrahedron Lett., 6237, (1966).
23. I. D. Webb and G. T. Borcherdt, J. Amer. Chem. Soc., 73, 2654 (1951).
24. E. J. Corey and E. K. W. Wat, J. Amer. Chem. Soc., 89, 2757, (1967).
25. E. J. Corey and H. A. Kirst, J. Amer. Chem. Soc., 94, 667, (1972).
26. M. F. Semmelhack, Org. React., 19, 115, (1972).
27. E. J. Corey and E. Hamanaka, J. Amer. Chem. Soc., 86, 1641, (1964).
28. E. J. Corey and E. Hamanaka, J. Amer. Chem. Soc., 89, 2758, (1967).
29. W. G. Dauben, G. H. Beasley, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle and C. Suter, J. Amer. Chem. Soc., 96, 4724, (1974).
30. E. J. Corey and K. C. Nicolaou, J. Amer. Chem. Soc., 96, 5614, (1974).
31. P. Busch and P. R. Story, Synthesis, 181, (1970).
32. P. R. Story, D. D. Denson, C. E. Bishop, B. C. Clark, Jr. and J-C. Farine, J. Amer. Chem. Soc., 90, 817, (1968).
33. I. J. Borowitz, G. J. Williams, L. Gross and R. Rapp, J. Org. Chem., 33, 2013, (1968), I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco and R. D. G. Rigby, J. Org. Chem., 37, 581, (1972).
34. I. J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby and S-N. Ueng, J. Org. Chem., 38, 1234, (1973).
35. I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G. J. Williams, J. Org. Chem., 31, 3032, (1966).
36. J. R. Mahajan, G. A. L. Ferreira and H. C. Araujo, Chem. Commun., 1078, (1972). J. R. Mahajan, G. A. L. Ferreira, H. C. Araujo and B. J. Nunes, Synthesis, 313, (1973).
37. P. S. Wharton, J. Org. Chem., 26, 4781 (1961).
38. M. Tanabe and D. F. Crowe, Tetrahedron Lett., 2955, (1964).
39. a) P. S. Wharton and G. A. Hiegel, J. Org. Chem., 30, 3254, (1965); b) C. A. Grob in "Theoretical Organic Chemistry, Report on the Kekulé Symposium," Butterworths, London, 1958, P. 114. C. A. Grob, Angew. Chem. (Int. Ed. Engl.), 8, 535, (1969). C. A. Grob, H. R. Kiefer, H. Lutz and H. Wilkens, Tetrahedron Lett., 2901, (1964).
40. P. S. Wharton, Y. Sumi and R. A. Kretchmer, J. Org. Chem., 30 234, (1965).
41. J. A. Marshall and C. J. V. Scanio, J. Org. Chem., 30, 3019, (1965).
42. J. A. Marshall and G. L. Bundy, J. Amer. Chem. Soc., 88, 4291, (1966). J. A. Marshall, Synthesis, 229, (1971).

43. P. S. Wharton, C. E. Sundin, D. W. Johnson and H. C. Kluender, J. Org. Chem., 37, 34, (1972).
44. E. J. Corey, R. B. Mitra and H. Uda, J. Amer. Chem. Soc., 86, 485, (1964).
45. J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalvoda, H. Kaufmann, P. Wieland and G. Anner, Helv. Chem. Acta, 50, 2101, (1967). P. Wieland, H. Kaufmann and A. Eschenmoser, Helv. Chem. Acta, 50, 2108, (1967).
46. A. Eschenmoser, D. Felix and G. Ohloff, Helv. Chim. Acta, 50, 708, (1967). D. Felix, J. Schreiber, G. Ohloff and A. Eschenmoser, Helv. Chem. Acta, 54, 2896, (1971).
47. N. J. Leonard, S. Swann, Jr. and E. H. Mottus, J. Amer. Chem. Soc., 74, 6251, (1952).
48. N. J. Leonard, S. Swann, Jr. and G. Fuller, J. Amer. Chem. Soc., 76, 3193, (1954).
49. N. J. Leonard, S. Swann, Jr. and H. L. Dryden, Jr., J. Amer. Chem. Soc., 74, 2871, (1952).
50. P. M. Baker, B. W. Bycroft and J. C. Roberts, J. Chem. Soc., C, 1913, (1967).
51. D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber and N. L. Wendler, Tetrahedron, 24, 2443, (1968). I. Vlattas, I. T. Harrison, L. Tökés, J. H. Fried and A. D. Cross, J. Org. Chem., 33 4176, (1968).
52. H. L. Wehrmeister and D. E. Robertson, J. Org. Chem., 33, 4173, (1968).
53. E. W. Colvin, T. A. Purcell and R. A. Raphael, Chem. Commun., 1031, (1972).
54. J. D. White, S. N. Lodwig, G. L. Trammell and M. P. Fleming, Tetrahedron Lett., 3263, (1974).

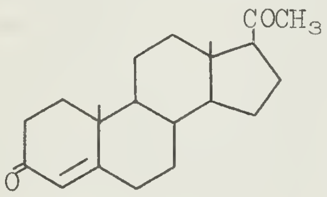
THE WISWESSER LINE-FORMULA CHEMICAL NOTATION: A NOVEL APPROACH TO SEARCHING CHEMICAL LITERATURE

Reported by William Todsen December 5, 1974

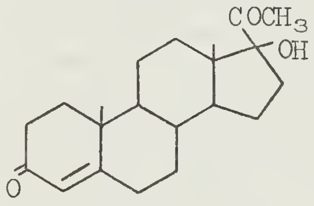
The Wiswesser Line-Formula Chemical Notation, or WLN, is a means of representing the structure of molecules by a linear sequence of symbols. It is thus related to the familiar structural diagrams chemists have used for over a century. WLN is just one of a broad spectrum of "nonconventional" ways of representing chemical structures; the three major classifications are fragmentation codes, nonunique topological codes, and linear notations. These methods are in contrast to the "conventional" systems: structural diagrams and nomenclature.[1] The basic motivation behind all these techniques is chemical information storage and retrieval (CISR).[2-5]

The difficulties associated with nomenclature are apparent to almost anyone who has tried to find a fairly complex structure in the literature or who has produced a new compound and tried to name it according to IUPAC conventions. Besides the complex hierarchy of rules, there are a number of exceptions and "trivial" nomenclature which enjoy widespread use despite their nonsystematic nature. These factors often conspire to make searching of literature (especially older literature, before the IUPAC rules were formulated) a rather laborious task. And even this assumes that a structure is well-defined - an attempt to search for a certain substructure is so formidable a problem that it is usually abandoned or simply never begun. Finally, unlike the structural diagram, which is the chemist's "universal language," names are different in different tongues.

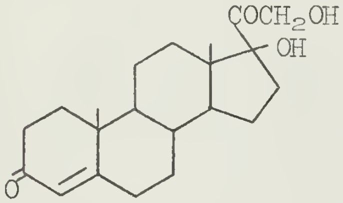
An example of these nomenclatural problems is shown below. Structure 1 is progesterone, and 4 is hydrocortisone; 2 and 3 represent intermediate degrees of hydroxylation. It is not entirely clear where to draw the line for naming 2 and 3. In Wiswesser notation, as will be seen later, this problem cannot arise. Since all four compounds have the same basic ring structure, they are classified together in an alphabetical list of notations.



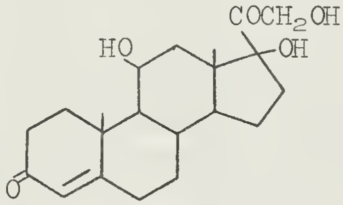
1



2



3



4

HISTORICAL

To avoid the difficulties of nomenclature, molecular formula indexes were introduced. However, this merely traded one ambiguity for another, since isomers have the same formula. Very simple substructure searches could be performed, such as determining if a molecule had three chlorine atoms, but absolutely no information could be obtained concerning the structural relationship of the atoms in the molecule. Therefore, additional search time was required to eliminate the undesired structures. These limitations in turn resulted in the development of fragmentation codes, which used tens of thousands of substructure terms.

Early CISR systems relied on punched cards, following the "one hole -- one meaning" approach. Fragmentation codes were assigned to particular punching positions. The presence of a hole implied the presence of that structural fragment. One such code, on which many present-day ones are based, was the CBCC (Chemical-Biological Coordination Center) code developed in 1946.[1] Besides the problem of substructure duplication due to the large number of known compounds was the serious limitation that fragments per se give no indication as to how the pieces fit together. Finally, as the number of compounds on file reached ca. 50,000, the physical bulk of the cards made them rather unwieldy.

Topological codes, which became more popular with advances in computer technology, describe molecular topology. This includes the number and size of rings, number of branches in chains, and chain length. One such code appeared about 1966 in the form of J T Baker Chemical Company's BATCH directory.[6] A modification of the topological approach is the connection table or connectivity matrix, which shows how each atom is bonded to every other atom, as well as the types of atoms involved. Although each matrix defines only one compound (it is unambiguous), there are many possible matrixes for each compound (the matrix is not unique). Also, a large amount of storage space is required and encoding is fairly slow, making the technique rather uneconomical. A streamlined version developed for computer manipulation of structural information has been described by Lefkovitz.[7-9]

The final major nonconventional system is linear notations (LN).[1,10-13] These are "strings" of characters which indicate the structure of a molecule. The major LN are both unique and unambiguous, and include such systems as the Wiswesser,[14-17,59] Dyson-IUPAC,[18] Hayward,[19,20,60] Silverton,[21] and Skolnik.[22] With the advent of the computer, very fast chemical information processing has been effected using LN: since they are linear the codes are easily "read" by computers, and because they are concise they require much less storage space. They are widely used for both documentation and substructure searching.[23-34] The two most highly developed LN are the Dyson-IUPAC and Wiswesser notations, each named after its inventor.[1,35]

The Dyson notation, developed in 1944 by Dr. G. M. Dyson, was adopted as the "official" IUPAC code at a time (1958) when other LN were in their infancy. Presumably IUPAC felt it was better to have some official notation system than to wait for other relatively untried codes to mature. A final revision of the Dyson-IUPAC code was made in 1961.[18] Chemical Abstract Service was one of the first large-scale users of Dyson notation: they encoded all the compounds in Chemical Abstracts and Beilstein, some 1.5 million in 1961. Unfortunately, because the notation required use of super- and subscripts as well as such special characters as underlining, the equipment for card punching and reading for computer implementation had to be specially ordered at a cost of several million dollars.

The Wiswesser notation (WLN) was first conceived in 1952 by Mr. W. J. Wiswesser. The first manual for encoding was published in 1954.[36] As use became more widespread, problems began to appear, and a group of WLN users formed the Chemical Notation Association to revise the rules for the code in 1965. Their practical experiences were codified in a revised form of the WLN manual published in 1968.[17] The revision was authored by Dr. E. G. Smith of Mills College, Oakland, California; the step-by-step approach employed in the new manual lends itself very well to learning the notation through self-study. Two great advantages which WLN possesses are the following: first, all 40 symbols used (letters A-Z, numerals 0-9, and & - / and blank space) are available on standard punched-card machines and computers. Second, since the space is a significant character (it effectively doubles the character set), most Wiswesser notations are broken up into word-like chunks which are much more readable for people. By virtue of its concise, unambiguous, unique nature, WLN is extremely valuable for CISR systems. Finally, unlike nomenclature systems, the structure codes are invariant with time and language (unless, of course, the structure itself is revised!).

USES OF WLN IN CISR

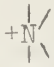
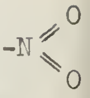
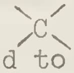
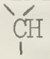
The limitations of nomenclature as a documentation and structure-searching tool have been described. However, computers in combination with linear notations such as WLN have allowed unprecedented ease of chemical structure information handling. Since structural diagrams themselves are hard to input, store, and manipulate by computer, the several coding schemes described earlier were developed;[20,37-41] linear notations have enjoyed special prominence in this area. The two major uses of LN for CISR systems is for documentation and substructure searching. In the former, one must search a file to see if a structure has already been assigned a place, and if not, it must be assigned an identifying number and integrated into the file. WLN is often used for this purpose,[61] so there must be some means of verifying encoding accuracy. One method, developed by Bowman and co-workers, calculates the molecular formula from the notation and compares it with one given as input.[42] Another, particularly useful for very complex ring systems, generates the canonically correct WLN from a connectivity matrix.[43] The simplest input method for the average organic chemist would be to just draw the structures, of course. Programs developed by Koniver and associates at National Institutes of Health do exactly that: a structure drawn on a Rand tablet is converted by the computer to WLN; this can then be further used for searching a large compound file by computer.[44-48]

Most chemists do not have access to these advanced computer systems yet still desire or require rather sophisticated substructure searches. Here WLN shows its great versatility as an easily "people-readable" as well as computer-readable code. Alphabetized lists of Wiswesser notations provide useful manual search tools. However, many significant symbols are "buried" in the symbol string, and because they do not initiate the line, alphabetization scatters them throughout the list. Computers have again come to the rescue. Programs have been written which "permute" or shift the symbol strings so that previously buried significant symbols *do* initiate the string. When such permuted strings are then alphabetized, all of the compounds containing a particular function are brought together in one place in the telephone directory-like index.[49-55] This permutation and alphabetization is called KWIC (keyword in context) indexing, and is used in such familiar publications as *Chemical Titles*. Permuted notation "directories" greatly facilitate substructure searches. By including an identifying number with each notation, reference can then be made to more complete descriptions such as the compound name, physical properties, and literature references. One such system is available in the Chemistry Library: it is called the Chemical Substructure Index, and will be discussed in more detail below. To make use of these manual indexes, a rudimentary knowledge of WLN is very helpful, and this is the problem which will be discussed presently.

CONVERTING WLN TO STRUCTURES: DECODING THE NOTATION.

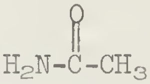
Wiswesser notation is a very useful tool for substructure searching, both manually (through permuted indexes) and by computer. The code is used by more than 100 organizations, representing a structure pool of well over a million compounds. First it should be emphasized that decoding is much easier than encoding, because it is necessary neither to determine the unique code for a compound nor to find the proper path through a complex structure: this has already been done by the encoder! The code is based on the longest possible continuous chain of atoms in a structure that produces meaningful indexing; that is, the "principle of least effort". Accordingly, almost all international chemical symbols are retained, and only about a dozen new symbols (mostly for functional groups) are introduced. The WLN "alphabet" is given below; an asterisk indicates a "new" symbol.

A	generic Alkyl
B	boron
P	phosphorus
Q* @	hydroxyl group, -OH (aQua)

C	(unbranched) carbon
D*	chelates and Dentate bonds
E*$^{@}$	bromine (Evil liquid)
F$^{@}$	fluorine
G*$^{@}$	chlorine (Greenish Gas)
H$^{@}$	hydrogen
I$^{@}$	iodine
J*$^{@}$	generic halogen; also terminates ring descriptions
K*	tetravalent nitrogen, +N 
L*	starts carbo- or aLicyclic ring descriptions
M*	imino group, -NH-
N	nitrogen
O	oxygen
R*	benzene Ring
S	sulfur
T*	begins heTerocyclic ring descriptions; describes ring saturation
U*	Unsaturation (UU=triple bond)
V*	carbonyl group, > C=O
W*$^{@}$	branched dioxo group, e.g., -N 
X*	carbon bonded to four other atoms: 
Y*	carbon bonded to three other atoms: or 
Z*$^{@}$	amino group, $-NH_2$
NUMERALS	length of saturated unbranched alkyl chains; size of rings

Six elements, potassium, uranium, vanadium, tungsten, bromine, and chlorine, are assigned new symbols: -KA-, -UR-, -VA-, -WO-, E, and G. All two-letter atomic symbols are enclosed in hyphens, as -MG- = magnesium. Note that in alphabetical lists, all halogens will be brought together (E, F, G, I).

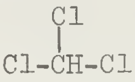
Basically, these symbols are joined together in the same order as in the compound they represent. Structures 5-7 merely require that the symbols be substituted with their structural counterparts.

Q2	$HO\text{-}CH_2CH_3$	ZV1	 $H_2N\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3$	WN1	$O_2N\text{-}CH_3$
5a	5b	6a	6b	7a	7b

If a branch (represented by X or Y for carbon, N or K for nitrogen, and the usual tri- or higher-valent symbols like P or -AS-) occurs, each branch is delineated. The end of each chain is then indicated by either an ampersand (&) or the symbol of a monovalent element or group. The latter are indicated with a superscript $^{@}$ in the above "alphabet." Structures 8 and 9 are examples.

GYGG

8a



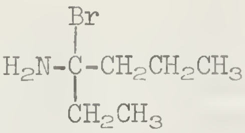
$Cl\text{-}\overset{\overset{Cl}{|}}{C}H\text{-}Cl$

8b

Note that "G" terminates one branch.

ZXE3&2

9a

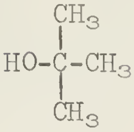
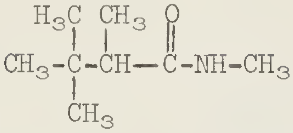


$H_2N\text{-}\underset{\underset{CH_2CH_3}{|}}{\overset{\overset{Br}{|}}{C}}\text{-}CH_2CH_2CH_3$

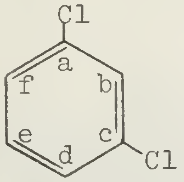
9b

In this case, "E" terminates one chain, and the ampersand terminates another.

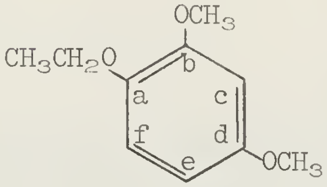
The symbols X, Y, and K are assumed to be methyl-branched unless explicitly indicated otherwise. This avoids cluttering the notation with the very common methyl "1" group to give a more concise and readable notation. Thus, if one of these symbols appears not to have enough substituents, it is because the "unfilled" positions are occupied by methyl. If there is more than one branch symbol, these "ghost" methyls are indicated with ampersands (implying the end of a chain). These principles are illustrated in 10 and 11. Since the benzene Ring is so common, it is given a single-letter symbol (R) to conserve space. Instead of numbers, as in conventional nomenclature, WLN uses a letter preceded by a space to LOCATE the substituents on a ring. (Remember that the space is used as a "shift key" to produce a LOwer CAse letTEr.) The chain cited before

WLN:	QX	1X&&YVM1
"expanded" WLN:	QX1&1&1	1X1&1&Y1&VM1
structure:	 $HO{-}\overset{CH_3}{\underset{CH_3}{C}}{-}CH_3$ 10	 $CH_3{-}\overset{H_3C}{\underset{CH_3}{C}}{-}\overset{CH_3}{CH}{-}\overset{O}{\overset{\Vert}{C}}{-}NH{-}CH_3$ 11

the "R" is assumed to be attached at locant "a". Thus 12 and 13 show the use of these alphabetical locants to show the position of substituents.

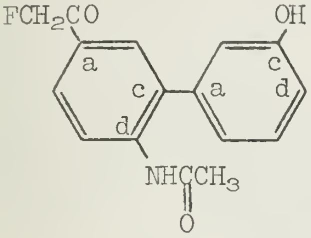


12: GR CG

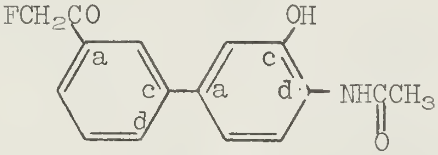


13: 20R B01 D01

Since benzene rings may have several substituents, ampersands are sometimes necessary to indicate the proper point of attachment. Thus 14a, not 14b, is the correct structure for the code: F1VOR CR CQ& DMV1



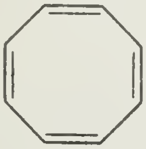
14a



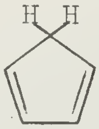
14b

The letter locants (space/letter combination) introduced for benzene rings is also used to place substituents on other types of rings. Special descriptive sequences are required for these potentially more complex rings; such "ring descriptions" start with an L (carbocycles) or T (heterocycles) and in all cases end with the symbol J. After the ring description are shown the substituents and their locants. Within the L...J or T...J symbols first come numerals showing the size of the ring(s). For heterocyclic systems, ring "stituents" (atoms in the ring itself) are indicated next. Finally, the saturation of the ring system is indicated. Carbocyclic monocycles will be considered first.

If a ring is completely unsaturated, either no "U" or "H" symbols will be shown, or the single extra hydrogen will be indicated, as in 15 and 16.

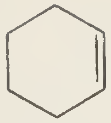


15: L8J

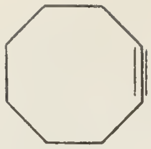


16: L5 AHJ

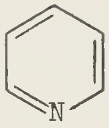
If the ring is completely saturated, a "T" will precede the closing "J". In this case, any unsaturations must be explicitly stated using "U", as in 17 and 18. These same principles for unsaturation apply to heterocyclic monocycles, but in addition the ring stituents must be indicated, again using locants. Thus, 19 is pyridine and 20 is morpholine. Note the use of "M" for the -NH- stituent in 20.



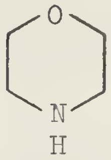
17: L6UTJ



18: L8UUTJ

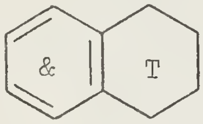


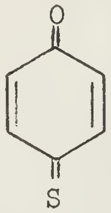
19: T6NJ



20: T6M DOTJ

Moving one step further, to bicyclic fused rings, the notation gives two numbers for the ring sizes. Unsaturations and ring stituents follow the general form outlined above for monocyclic rings, with one important addition: if one ring is saturated and the other is unsaturated, this is shown by T and & symbols, respectively, just before the closing J of the ring description. Structure 21 shows an example of this type. When a carbonyl is a ring stituent, it is indicated by the usual "V" within the ring signs. A "Y" within ring signs is always used to represent other exocyclic double bonds, as in the hemithioquinone 22. Note that the ring locant indicated within ring signs to be exocyclic will have a corresponding substituent outside the ring signs starting with _*U..., where * is the locant.

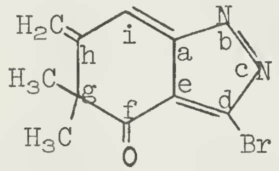




21: L66&TJ

22: L6V DYJ DUS

Finally, if ring stituents occupy consecutive locants in the ring, that is, if they are directly connected, no locants are cited between them. A ring system illustrating all these points is shown as 23. Note that methyl substituents (after the closing J of the ring description) are indicated by giving only the locant. The locant path is completed in the same order as the ring numeral order: it goes around the smaller ring first.



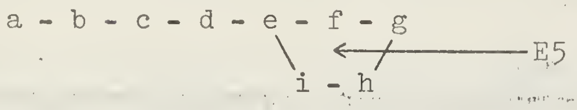
23: T56 BNN FV HY GHJ DE G G HU1

Polycyclic fused rings systems such as those found in steroids are an extension of the same principles used above for other less complex examples. For instance, progesterone (1) would be assigned the Wiswesser notation: L E5 B666 OV MUTJ A E FV1. The structural similarity of compounds 1-4 is clearly evidenced by their similar WLN codes; it will be recalled that nomenclature was rather inefficient in this respect.

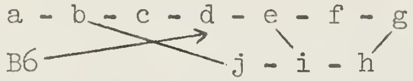
structure	WLN
1	L E5 B666 OV MUTJ A E FV1
2	L E5 B666 OV MUTJ A E FV1 FQ

3 L E5 B666 OV MUTJ A E FV1Q FQ
4 L E5 B666 OV MUTJ A CQ E FV1Q FQ

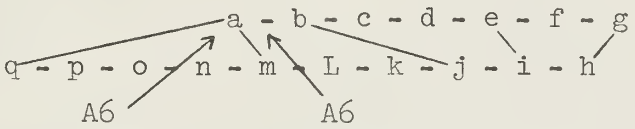
To illustrate decoding these polycyclic structures, the code for 1 will be used. The first ring numeral after the opening "L" is a five, and it is preceded by a locant "e". Therefore, first write a chain of consecutive letter locants and close a ring with "e" as the earliest locant:



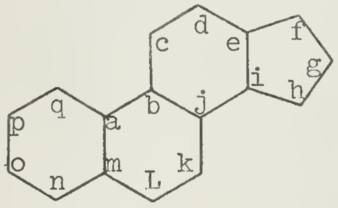
The next ring numeral is a six, preceded by locant "b", so close a six-membered ring with "b" as the earliest locant:



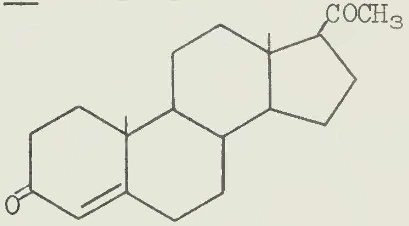
The last two ring numerals (two 6's) do not have any locant preceding them, so their earliest locant is assumed to be "a". Therefore, extend the chain again so that two six-membered rings can be closed, both with "a" as the first locant. The end result is four rings: efghi, bcdeij, abjkLm, and amnopq. Note that locant "L" is capitalized to distinguish it from the numeral "1". By rearranging and "puckering" the locants, the more conventional appearance can be obtained;


a - b - c - d - e - f - g
q - p - o - n - m - L - k - j - i - h
A6
A6

this is shown as 1a. The notation indicates a carbonyl group at position "o" (_OV) and a double bond from "m" to "n" (_MU), as well as the fact that except for this unsaturation, all the rings are saturated (T just before closing J). Methyl groups are indicated for positions "a" and "e", following the ring description; a -CO-CH_3 group is shown by the notation to be situated at position "f" (_FV1). These data give the structure 1b for progesterone.



1a



1b

More complex structures, such as those containing spiro atoms, so-called multicyclic points (perifused systems), and bridges, as well as chains of several ring systems, can also be distinctively encoded in Wiswesser notation. Those interested in these rarer ring types are referred to the WLN manual.[17]

CHEMICAL SUBSTRUCTURE INDEX

It was mentioned above that modern computer processing techniques have made permuted (KWIC) indexes of notations feasible. One very useful directory of this type is the Chemical Substructure Index (CSI), published by the Institute for Scientific Information. (ISI also publishes the Citation Index.) Monthly issues and annual cumulations give Wiswesser notations for all of the compounds which have appeared in Current Contents of Chemistry and Index Chemicus since 1967. Even with only the rudiments of WLN presented in this abstract, one can use CSI to rapidly locate compounds and/or fragments of specific interest. CSI is also useful for "browsing" for compounds which are structurally similar to the one of interest, particularly as more familiarity with WLN is attained.

There are three ways to use the versatile Chemical Substructure Index. The first is through a detailed knowledge of Wiswesser notation. The code for

16. G. Palmer, Chem. Brit., 6, 422 (1970).
17. E. G. Smith, "The Wiswesser Line-Formula Chemical Notation," McGraw-Hill, 1968.
18. International Union of Pure and Applied Chemistry, "Rules for IUPAC Notation for Organic Compounds," Wiley, New York, 1961.
19. H. W. Hayward, H. M. S. Sneed, J. H. Turnipseed, S. J. Tauber, J. Chem. Doc., 5, 183 (1965).
20. B. A. Marron, G. R. Bolotsky, S. J. Tauber, ibid., 6, 92 (1966).
21. E. Silverton, R. F. Pasternak, J. Res. NBS, sect. A, 70, 23 (1966).
22. H. Skolnik, J. Heterocycl. Chem., 6, 689 (1969).
23. G. A. Miller, J. Chem. Doc., 12, 60 (1972).
24. A. Leo, D. Elkins, C. Hansch, ibid., 14, 61 (1974).
25. D. Elkins, A. Leo, C. Hansch, ibid., p. 65.
26. L. H. Thomson, E. Hyde, F. W. Matthews, ibid., 7, 204 (1967).
27. E. Hyde, F. W. Matthews, L. H. Thomson, W. J. Wiswesser, ibid., p. 200.
28. E. Hyde, F. W. Matthews, L. H. Thomson, AGARD Adv. Rep., 1968, 28. Cf. Chem. Abst., 71, 18677b.
29. G. F. Fraction, J. C. Walker, S. J. Tauber, Nat. Bur. Std. (US), Tech. Notes, 1968, #432. Cf. Chem. Abst., 70, 34186a.
30. E. G. Smith, Science, 131, 142 (1960).
31. C. M. Bowman, F. A. Landee, N. W. Lee, M. H. Reslock, B. P. Smith, J. Chem. Doc., 10, 50 (1970).
32. C. M. Bowman, V. B. Bond, N. L. Lee, D. R. Peterson, M. H. Reslock, ibid., 11, 168 (1971).
33. J. E. Crowe, P. Leggate, B. N. Rossiter, J. F. B. Rowland, ibid., 13, 85 (1973).
34. R. J. Feldmann, S. R. Heller, ibid., 12, 48 (1972).
35. P. Fresenius, Pharm. Ztg., 118, 877 (1973).
36. W. J. Wiswesser, "A Line-Formula Chemical Notation," Crowell, New York, 1954.
37. E. Hoffman, Int. Conf. Inform. Sci. Proc., 1971, 755. Cf. Chem. Abst., 77, 113202a.
38. E. Hyde, Appl. Spectr., 21, 381 (1967).
39. M. F. Lynch, J. Orton, W. G. Town, J. Chem. Soc., sect. C, 1969, 1732.
40. E. Meyer, Angew. Chem., Int. Ed. English, 9, 583 (1970).
41. G. Szonyi, Abs. Pap. ACS, CHLT-18 (April-June 1974).
42. C. M. Bowman, F. A. Landee, M. H. Reslock, J. Chem. Doc., 7, 43 (1967).
43. C. M. Bowman, F. A. Landee, N. W. Lee, M. H. Reslock, ibid., 8, 133 (1968).
44. S. R. Heller, D. A. Koniver, ibid., 12, 55 (1972).
45. D. A. Koniver, C. D. Farrell, A. R. Chauvenet, ibid., 11, 52 (1971).
46. D. A. Koniver, R. J. Feldmann, ibid., p. 154.
47. D. A. Koniver, W. J. Wiswesser, E. Usdin, Science, 176, 1437 (1972).
48. J. R. Snyder, Abs. Pap. ACS, CHLT-4 (September 1970).
49. A. Gelberg, J. Chem. Doc., 6, 60 (1966).
50. C. E. Granito, A. Gelberg, J. E. Schultz, G. W. Gibson, E. A. Metcalf, ibid., 5, 52 (1965).
51. C. E. Granito, J. E. Schultz, G. W. Gibson, A. Gelberg, R. J. Williams, E. A. Metcalf, ibid., p. 229.
52. J. K. Horner, ibid., 7, 85 (1967).
53. A. E. Petrarca, M. J. Lee, Abs. Pap. ACS. CHLT-7 (September 1971).
54. A. E. Petrarca, W. V. Laitinen, W. M. Lay, J. Chem. Doc., 11, 148 (1971).
55. P. F. Sorter, C. E. Granito, J. C. Gilmer, A. Gelberg, E. A. Metcalf, ibid., 4, 56 (1964).
56. C. E. Granito, M. D. Rosenberg, ibid., 11, 251 (1971).
57. Patterson, Capell, Walker, The Ring Index, American Chemical Society, 1960 and supplements.

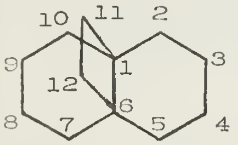
58. Chemical Abstracts Service, American Chemical Society, Clearinghouse publication #PB180901 (1968).
59. J. P. Mitchell, Proc. WLN Mtg., Army CIDS Prog., Clearinghouse publication #AD665397 (1968).
60. HAYSTAQ search system of U.S. Pat. Off. *Cf*. Chem. Abst., *64*, 7336f.
61. C. E. Granito, D. E. Renard, L. A. Holly, J. Chem. Doc., *6*, 252 (1966).

RECENT DEVELOPMENTS IN PROPELLANE CHEMISTRY

Reported by David B. Reitz December 9, 1974

INTRODUCTION

Propellanes are tricyclic systems cojoined by a carbon-carbon single bond. Although propellanes have been known since 1938,[1] until recently they have not been subjected to systematic study. In 1964, Vogel[2] synthesized [4.4.1]propellanes in order to investigate their conversion to substituted [10]annulenes. That same year Bloomfield[3] published work on the unsuccessful conversions of [4.4.3]propellanes to substituted [10]annulenes. In 1966, Bloomfield[4] suggested the trivial name "propelleranes" for these compounds, because of their resemblance to propellers. Likewise, in 1966, Ginsburg[5] published the first of his many papers on the synthesis of these tricyclic compounds and advanced the trivial name "propellane". According to Ginsburg's nomenclature system, the compound is numbered starting with one of the bridgehead atoms, proceeding by the longest direct route to the second bridgehead atom, returning to the first bridgehead atom by the next longest route, and finally proceeding to the second bridgehead atom by the remaining route. The common cojoining bond is not counted but is implied in the root name "propella". This nomenclature system is exemplified below.



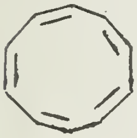
[4.4.2]propellane

Spectral studies on various propellanes have been carried out. Kunai and co-workers[6] have done mass spectral studies, Weinges and Wiesenhutter[7] have compiled nmr chemical shift values, and Gleiter, Paquette, and co-workers[8] have recorded the photoelectron spectra of polyunsaturated [4.4.2]propellanes. Birnbaum and co-workers[9] and Ermer and co-workers[10] have done X-ray studies on [4.4.3] and [4.4.4]propellanes, respectively.

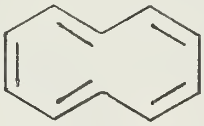
The synthesis of propellanes has been the subject of much interest[11-15] and has been thoroughly reviewed.[16-18] Consequently, this review will cover only the reactions of propellanes.

PROPELLANES AS PRECURSORS TO ANNULENES

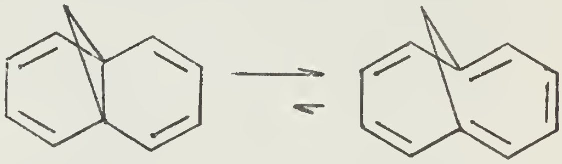
[10]Annulenes may exist in two possible geometries, the all-cis-configuration 1, and the more familiar, less symmetrical structure with two trans double bonds 2. The former geometry has bond angles of 144° possessing undue Baeyer strain while the latter suffers from a severe interaction of the two internal hydrogens. Vogel[19] recognized that substitution of a methylene group for the two internal hydrogens would allow for considerable flattening of the C_{10}-framework, thus facilitating aromaticity, and approached the synthesis of [10]annulenes through its valence bond isomer a [4.4.1]propellatetraene. This propellane can be looked upon as a "double norcaradiene". As expected, this propellane was unstable and spontaneously rearranged to the 1,6-methano-[10]annulene (2a) in high yields.



1



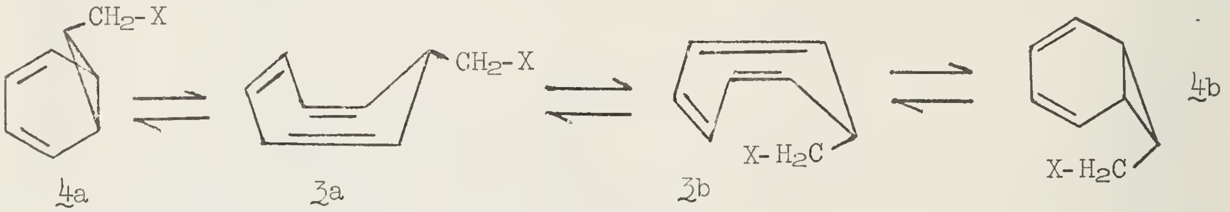
2



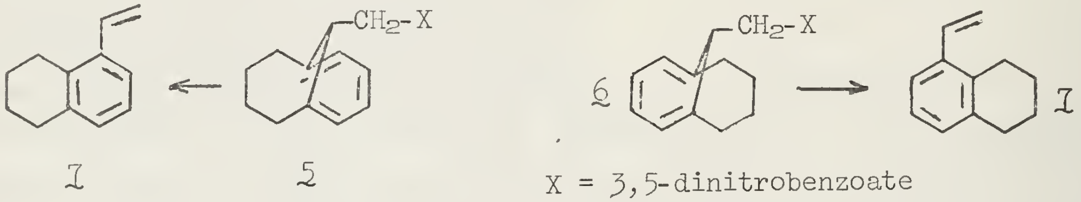
2a

SOLVOLYTIC STUDIES OF PROPELLANES

In 1967, Sargent and co-workers[20] studied the solvolysis of 7-cyclohepta-1,3,5-tri-enylcarbinyl 3,5-dinitrobenzoates and demonstrated that ionization can be preceded and perhaps even initiated by valence isomerization. In further studies, Paquette[21] pursued the question as to whether ionization occurs preferentially from the thermodynamically more stable conformer 4a or from conformer 4b in which the electron deficient center could profit from remote pπ stabilization. Annulation of the cycloheptatriene system transforms interconvertable conformers into non-interconvertable isomers; thus making it possible to analyze what effect conformation has on the rate of solvolysis.

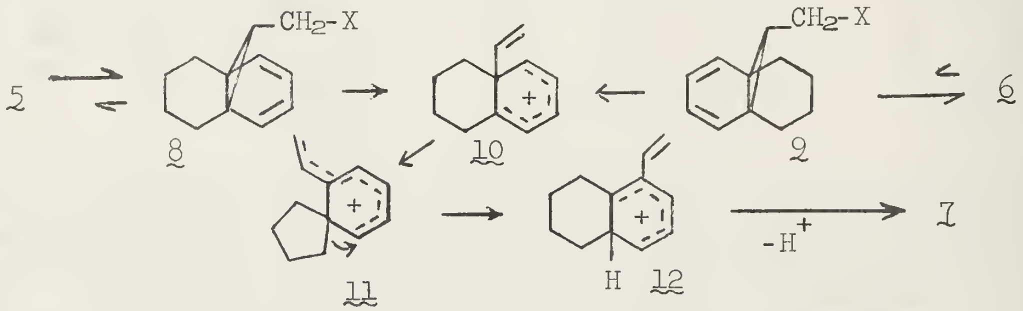


The solvolysis of 5 or 6 in 80% acetone/water (v/v) buffered with 2,6-lutidine at 70-115° produces 5-vinyltetralin (7) in 99% yield. Paquette observed that the anti isomer 6 reacted 3.4 times faster than did the syn isomer 5. Paquette claims his data clearly supports the Sargent proposal that ionization reactions of 7-cycloheptatrienylmethyl derivatives proceed through the norcaradienylcarbinyl valence isomer and are cyclopropyl assisted. Because of the similarity in rates of solvolysis, Paquette believes that solvolysis of 5 and 6 are dependent upon the operation of a pre-equilibrium involving 8 and 9, respectively. Thus, the observed rate constants are comprised of pseudo-first-order rate and equilibrium constants.



X = 3,5-dinitrobenzoate

Paquette proposes that 10→11→12→7 is the most likely pathway to 7 because intermediate 11 offers the greatest degree of π delocalization, and many closely related spirocyclic processes are known.[22] However, he does not dismiss other options such as vinyl migration or π alkylation.

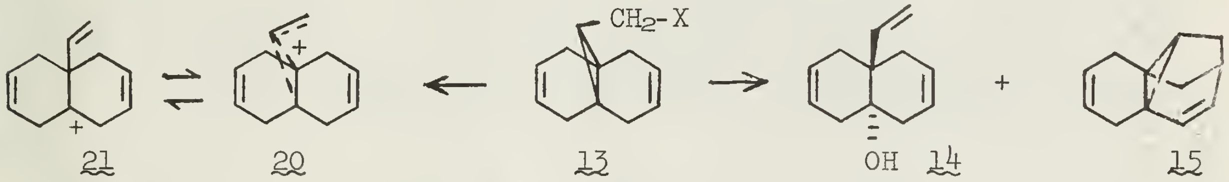


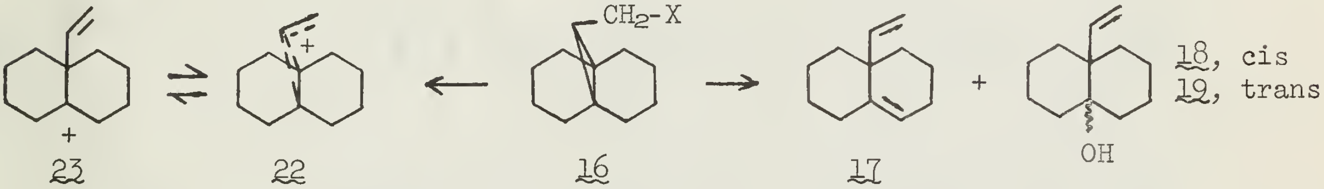
In a related study, Warner and Lu[23] conducted solvolysis studies on a series of [4.3.1]propellanes which exist "exclusively" in the norcaradiene form, thus eliminating the pre-equilibrium problem encountered by Paquette.

They observed good first-order kinetics in all cases and found that the anti-10-hydroxymethyl[4.3.1]propella-2,4-diene 3,5-dinitrobenzoate reacted 80 times faster than the syn isomer.

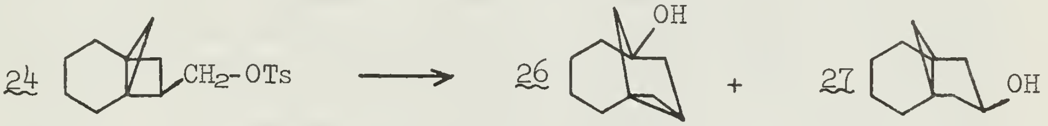
Solvolysis of the related propellane 16 in 80% acetone/water (v/v) produces 17 (65%), 18 (15%), and 19 (19%) while the solvolysis of 13 produces 14 (77-91%) and 15 (23-9%).[21] The amount of 15 increases with time. The kinetic data reveal a tenfold increase in rate for 16 as compared to 13. This value agrees with the factor estimated for the inductive contributions of two β-orientated double bonds by Sargent.[20]

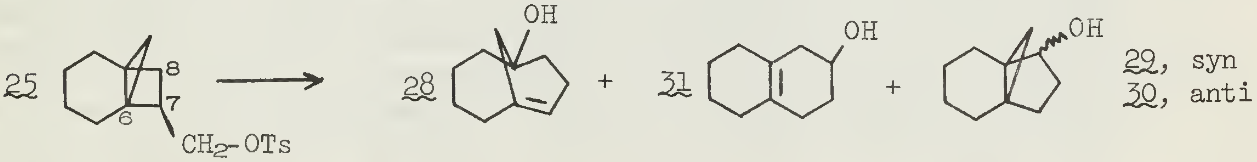
Drawing on analogy,[24] Paquette suggests that the ionization of 13 may be represented as the departure of the leaving group with the generation of a delocalized cationic intermediate 20 which is in equilibrium with the homoallylic cation 21. He believes that the differing stereoselectivity of solvent capture arises from a reversal of the stability orders for the 20:21 and 22:23 pairs. Possibly, the greater conformational driving force of the cyclohexyl rings to adopt chair-like arrangements may be sufficient to make the bridged species 22 less energetically favorable than the open ion 23.



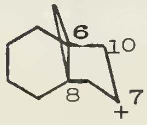


Gassman[25] has studied the solvolysis of syn and anti-7-hydroxymethyl[4.2.1]-propellane p-toluenesulfonates. When solvolysed, these systems should produce annulated cyclobutylcarbinyl cations. The kinetic data showed that the rates of solvolysis for both epimers were very similar. In contrast, a detailed product study indicated a high degree of involvement by the rest of the molecule in ionization. Solvolysis of 24 in 90:10 (v/v) acetone/water yielded 26 (91%) and 27 (5%). This was the kinetic product mixture, since treatment with acid produces an equilibrium mixture of 55% 26 and 45% 27. Solvolysis of 25 produced 28 (56%), 29=30 (12%), and 31 (11%) when buffered with 2,6-lutidine. It was demonstrated that 28, 29, and 30 are readily converted to 31 in the presence of acid, and the solvolysis gave only 31 when unbuffered. Gassman explains the product distribution in terms of a stereospecific rearrangement. He contends that ionization of 24 with C$_6$ migration leads to cation 32 which can be stabilized by the neighboring cyclopropyl ring as shown in 33, while 25 with C$_8$ migration leads to cation 34. Migration of C$_6$ in the solvolysis

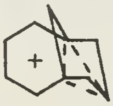




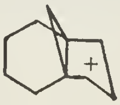
32



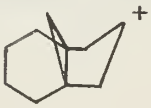
33



34



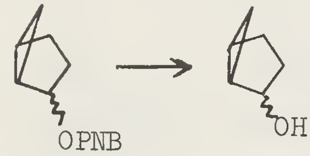
35



of 25 would produce 35 which is not well situated for stabilization by the neighboring cyclopropyl group.

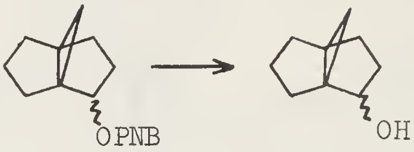
Gassman and co-workers[26] were interested in the question of whether different cations result from the ionization of a suitable leaving group from the exo and endo sides of the 2-position of the bicyclo[3.1.0]hexane nucleus. Solvolysis studies were done on bridged and unbridged bicyclo[3.1.0]-hexan-2-ol-p-nitrobenzoates. The bridging was at the 1,5 positions thus making the molecule a [n.3.1]propellane. The relative rates of solvolysis for compounds 36-41 in 70:30 (v/v) acetone/water are 1230:661:722:210:2.8:1.0. As one can see, bridging at the 1,5 position provides a considerable increase in solvolysis rates. However, examination of the epimeric pairs 40:41, 38:39, and 36:37 shows rate ratios of 2.8, 3.4, and 1.9, respectively. These small ratios suggest that the polymethylene bridges probably affect both the exo and endo p-nitrobenzoate in the same manner and that orientation of the ionized bond has little effect on the rate.

Product studies done on 38 or 39 at 100° reveal a 1:2 mixture of 42 and 43 on solvolysis in aqueous acetone for both epimers. However, product studies on 36 and 37 were somewhat more complicated, due to the instability of some of the products under reaction conditions. After ten half-lives at 85° 36 gave 28 (59%), 29 (5%), 30 (7%), and 31 (20%). As the product ratios for 37 were similar to 36, Gassman states that 36 and 37 probably ionize to give the same cationic intermediate.



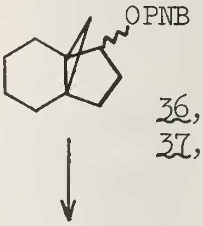
40, syn
41, anti

44, syn
45, anti



38, syn
39, anti

42, syn
43, anti



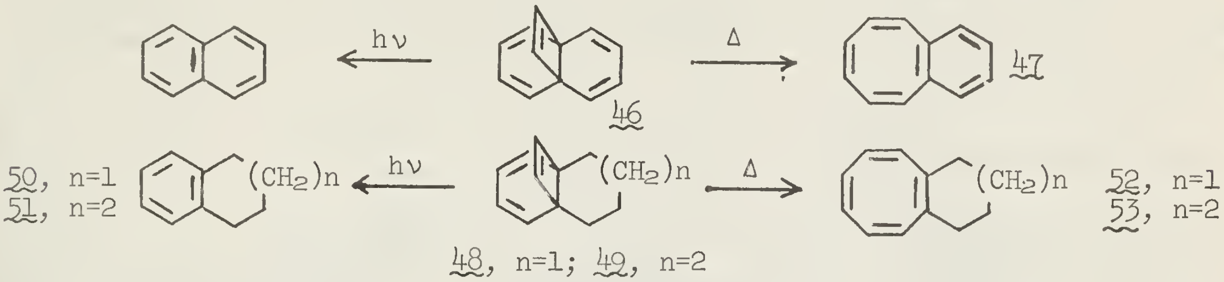
36, syn
37, anti

28 - 31

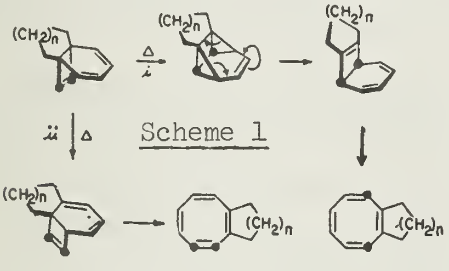
The significant difference in the primary products obtained from the structurally different propellanes is of interest. Alcohol 28 is the major product from 36 and 37 while the analogous product is absent from 38 and 39. This Gassman rationalized on the basis of Bredt's rule. The bridged nine-membered ring in 28 is able to sustain a trans double bond, while the analogous compound from 38 and 39 would have an eight-membered ring with a bridgehead double bond; this would involve sufficient strain energy as to inhibit formation of products of this type.

THERMOLYTIC AND PHOTOLYTIC REACTIONS OF PROPELLANES

Paquette and co-workers[27] have used propellanes in order to investigate the interactions of perpendicular π systems. Present theoretical description of bicycloaromaticity is founded upon through space interactions of perpendicular or nearly perpendicular π systems.[28] The sign discontinuity in the basis set of atomic orbitals present in propellapentaene 46 results in the operation of some electronic delocalization but no attendant stabilization.[8] In order to gain further insight into this question, annulated bicyclo[4.2.0] octatrienes such as 46, 48, and 49 were synthesized. Thermally allowed conrotatory rupture of the weak doubly allylic C-C bond cannot be obtained readily, and for reasons of orbital symmetry, photochemical cleavage in this mode is disallowe A real possibility now exists for cyclobutene ring cleavage in a $[{}_{\sigma}2_{s} + {}_{\sigma}2_{s}]$ fashion to give acetylenic and olefinic fragments, which is normally an energetically inaccessible reaction pathway. Translated into chemical reactivity terms this means that the cyclobutene ring in 46, 48, and 49 should be susceptible to fragmentation only under conditions of photochemical excitation, while under pyrolysis conditions an alternative lower energy process should be followed if available. When [4.4.2]propellapentaene (46) was irradiated with 253.7 nm light in ether solution (25°), rapid formation of naphthalene and acetylene ensued. However, gas-phase pyrolysis of 46 at 470° in a flow system under nitrogen resulted instead in skeletal rearrangement to benzocyclooctatetraene 47, which was isolated in 53% yield. Propellatrienes 48 and 49 behaved in an entirely comparable manner. Photolysis produced tetralin 50 and benzocycloheptene 51 with the loss of acetylene; flow pyrolysis produced the 1,2-annulated cyclooctatetraenes 52 (60% isolated) and 53 (47% isolated).

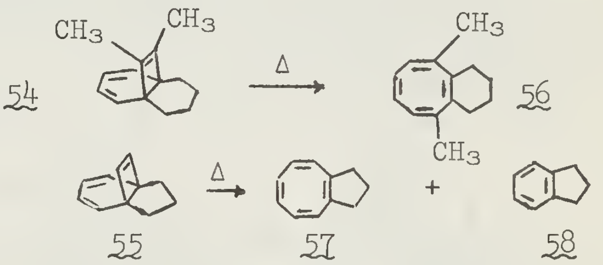


Although several hypothetical mechanisms can be advanced to explain the thermochemical rearrangements, Paquette considers two as most plausible as they maintain continuous orbital overlap throughout the bond relocation process. The first is an intramolecular [$_{\pi}4_s+_{\pi}2_s$] (Diels-Alder) cycloaddition of the perpendicular cyclobutene double bond with the cyclohexadiene moiety leading to a tetracyclo[4.2.0.0.^{2,8}.0^{5,7}]octene intermediate. This is followed by a six-electron reorganization within this newly formed bishomobenzene. An alternate mechanism would be an initial [1,5]-sigmatropic shift of a trigonal cyclobutene carbon atom followed by disrotatory opening of the newly formed bicyclo-[4.2.0]octatriene. Scheme 1 shows how deuterium labeling of the cyclobutene carbons can readily distinguish between these two mechanisms.



Scheme 1

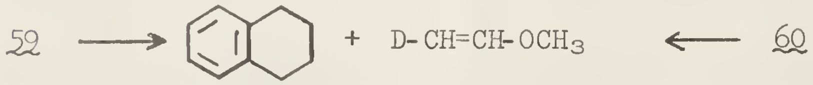
• denotes deuterium



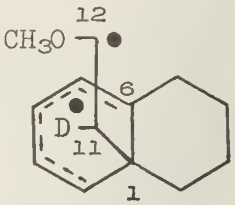
When the dideuterated propellane was pyrolyzed, the product was confirmed to be the 3,8-d$_2$ derivative by spectral comparison with an authentic sample prepared in an unequivocal fashion. These findings suggest exclusive operation of the [$_{\pi}4_s+_{\pi}2_s$] bond reorganization mode (path i).

If this mechanism is correct, then the reaction should depend in part upon the ability of the cyclobutene carbon atoms to flex somewhat in the direction of the adjoining diene unit. To test this hypothesis, propellanes 54 and 55 were pyrolyzed. At 430°, the dimethyl derivative 54 was completely unreactive; however, at 470° it did undergo rearrangement although in somewhat lower yield (50%). Propellane 55 was unusually stable. Only when temperatures were in excess of 600° did any reaction occur, producing low yields of 57 and 58 in 1:2 ratio. These results suggest that the increased bracketing strain progressively deters the capability of the cyclobutene sp^2 carbons to alter their relative position sufficiently to enter into tetracyclo[4.2.0.0^{2,8}.0^{5,7}]-octene formation.

Paquette and co-workers[29] have found that the thermal and photochemical fragmentations of the 11-deuterio-12-methoxy[4.4.2]propella-2,4-dienes are both stereoselective. The syn cis isomer 59 gives evidence of diminishing stereoselectivity in proceeding from pyrolytic to the photolytic reaction whereas the anti cis isomer 60 develops increased stereoselectivity.

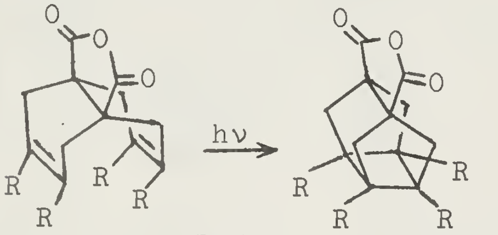


cis/trans		cis/trans
98/2	thermal (245°)	80/20
88/12	photochemical	98/2



61

Paquette explains the results by the following mechanism. In pyrolysis of syn-cis-11-deuterio-12-methoxy[4.4.2]propella-2,4-diene, (59), initial cleavage occurs at C_6-C_{12} bond. The resulting diradical 61 can either rotate around the C_{11}-C_{12} bond (k_{rot}) or the C_1-C_{11} bond can break (k_{scis}) forming tetralin and methoxyethene. The product ratio of cis and trans deuteriomethoxyethenes is determined by the k_{scis}/k_{rot} ratio. Paquette argues that C_{11}-C_{12} bond rotation in 61 would require the methoxyl group to migrate from a site over the planar diene where it is sterically unencumbered to a position over the tetramethylene bridge where serious compression with axially disposed methylene hydrogens will occur. In the corresponding diradical produced from 60 k_{rot} is larger and the stereoselectivity of the reaction is less. In the photolysis of 60, Paquette believes $[{}_{\sigma}2_s + {}_{\sigma}2_s]$cyclobutane fragmentation to be concerted in the manner anticipated from orbital symmetry considerations. To explain the lowered stereoselectivity in the photolysis of the syn isomer 59, he suggests that charge-transfer interactions of the proximate methoxyl group with the S_1 excited state of the cyclohexadiene ring could allow for the incursion of a modest amount of intersystem crossing ($S_1 \rightarrow T_1$) and subsequent stepwise fragmentation from the T_1 state.



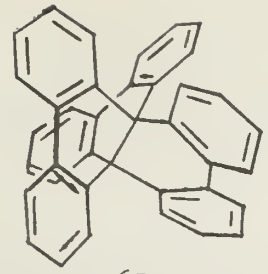
62 R=CH3 63

Avila and Silva[30] photolysed 3,4,8,9-tetramethyl-11,13-dioxo-12-oxa[4.4.3]-propella-3,8-diene (62) and produced 3,4,8,9-tetramethyl-tetracyclo-$[4,4,0,0,^{3,9},0^{4,8}]$decane-1,6-dioic anhydride (63). They proclaimed this to be the simplest synthesis of this tetracyclo-$[4,4,0,0^{3,9},0^{4,8}]$decane ring system. Subsequently, Ginsburg[31] has used this reaction in a structure proof.

REACTIONS OF OTHER PROPELLANE SYSTEMS

Through the use of dithia[n.3.3]propellanes, Weinges and Klessing[32] develope a synthetic route to 1,4-polymethylene bridged Dewar benzenes and their valence bond isomers [n]paracyclophanes. Using this procedure, the bridged Dewar benzene 64, (n=4) was isolated in 1% yield. The synthesis of these 3,7-dihetero[n.3.3]-propellanes and their nmr spectra are discussed in a separate paper.[7]

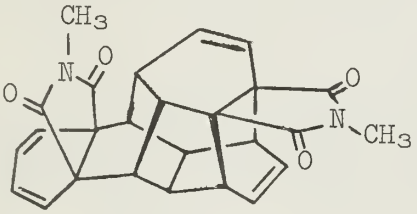
Wittig and Schoch[33] synthesized an aromatic [4.4.4]propellane to investigat whether or not the central bond could be cleaved by alkali metals to produce a radical anion or a dianion. Although the aromatic propellane 65 is twisted (see diagram), thus providing some degree of stabilization, the amount of π overlap was insufficient for radical or anion formation.



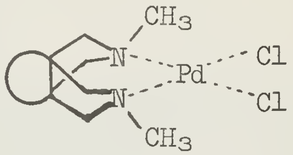
65

Ginsburg and co-workers[9] have made a series of bis and monoirontricarbonyl derivatives of 12-oxa[4.4.3]propella-2,4,7,9-tetraene. When the tetraenic ether was heated to reflux with diironnonacarbonyl five derivatives were isolated, two symmetrical bis compounds, one unsymmetrical bis compound, and two mono compounds. Their structure (syn or anti to ether) was determined by X-ray analysis of the bis syn derivative followed by removal of one irontricarbonyl with ceric ammonium nitrate.

Ginsburg and co-workers[34] have used INDOR spectroscopy to determine the structure of a dimer of 11,13-dioxo-12-methyl-12-aza[4.4.3]propella-2,4,7,9-tetraene. Heating the monomer in a melt (160°) afforded the dimer 66 in 80-90% yields. The mass spectrum of the dimer exhibited two important peaks besides the molecular ion, $(M^+, m/e=426)$, M^+-85 corresponding to the loss of $-CO-NCH_3-CO-$ and M^+-78, corresponding to the loss of benzene. The dimer is formed by an initial stereospecific (syn to imide) intermolecular Diels-Alder addition of monomer to itself followed by a second intramolecular Diels-Alder reaction. Ginsburg[35] has just reviewed the stereospecific reactions of propellanes.



66

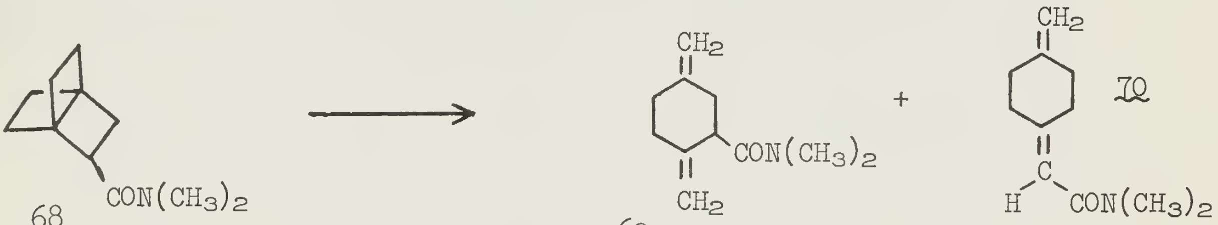


67

Ginsburg and co-workers[36] have found several 3,7-dimethyl-3,7-diaza[n.3.3]-propellanes to be highly selective chelating agents for palladium. The chelate complexes of type 67 were formed when the diazapropellanes were treated with palladium chloride. The azapropellanes reacted only with palladium, which may be due to steric limitations imposed by the relative rigidity of the propellanes.

REACTIONS OF HIGHLY STRAINED PROPELLANES

There has been considerable interest recently in the synthesis and properties of [2.2.2]propellanes. In 1973, Eaton and Temme[37] reported the first synthesis, isolation, and characterization of N,N-dimethyl[2.2.2]propellane amide (68). This very strained propellane is unstable thermally and undergoes first-order ring opening to a mixture (~9:1) of the unsaturated, monocyclic amides 69 and 70. The half-life for ring opening at 25° is 28 min. Very rapid halogen addition across the central bond was observed.



68 69 70

Wiberg and co-workers[38] claim to have synthesized the first [2.2.2]propellane hydrocarbon. They isolated 1,4-dimethylenecyclohexane when 1,4-dibromobicyclo-

[2.2.2]octane was reduced electrochemically. Wiberg believes this is clear evidence for the formation of [2.2.2]propellane. Wiberg and co-workers[39] have synthesized an organometallic[2.2.1]propellane, the most highly strained propellane prepared to date. This propellane is the bis(triphenylphosphine)platinum complex of $\Delta^{1,4}$-bicyclo[2.2.0]hexene. This air-stable compound reacts with ethanol at room temperature to afford an air-stable addition product with cleavage of the cojoining bond.

CONCLUSION

Because of their rigidity, propellanes have become increasingly useful in studying the effect structure has on reactivity. The use of propellane analogs of bicyclic structures has made it possible to selectively study similar reactions of different conformers. Propellanes have been used to study the interactions of perpendicular π systems. Propellanes have been employed to probe structure stability relationships, e.g. the equilibrium position between valence isomers as in the case of the norcaradiene-cycloheptatriene equilibrium. Utilization of this equilibrium has made propellanes the first successful precursors of [10]annulenes.

Recently, highly strained [2.2.2] and [2.2.1]propellane systems have been synthesized. The [2.2.2] system is thermally unstable and undergoes ring opening. The cojoining bond in both systems undergoes electrophilic addition.

BIBLIOGRAPHY

1. P. Brigl and R. Herrmann, Chem. Ber., 71B, 2280 (1938).
2. E. Vogel and H. D. Roth, Angew. Chem., Int. Ed. Engl., 3, 228 (1964).
3. J. J. Bloomfield and W. T. Quinlin, J. Amer. Chem. Soc., 86, 2738 (1964).
4. J. J. Bloomfield and J. R. S. Irelan, Tetrahedron Lett., 2971 (1966).
5. D. Ginsburg, Tetrahedron, Suppl. 8, Part 1, 279 (1966).
6. A. Kunai, T. Ishii, and Y. Odaira, Chem. Lett., 315 (1974).
7. K. Weinges and A. Wiesenhutter, Justus Liebigs Ann. Chem., 746, 70 (1971).
8. R. Gleiter, E. Heilbronner, L. A. Paquette, G. L. Thompson, and R. E. Winga Jr., Tetrahedron, 29, 565 (1973).
9. K. B. Birnbaum, J. Altman, T. Maymon, and D. Ginsburg, Tetrahedron Lett., 2051 (1970).
10. O. Ermer, R. Gerdil, and J. D. Dunitz, Helv. Chim. Acta, 54, 2476 (1971).
11. L. A. Paquette and G. L. Thompson, J. Amer. Chem. Soc., 94, 7118 (1972).
12. H. D. Martin and H. Mirko, Synthesis, 667 (1973).
13. C. S. Angadiyavar, J. Cornelisse, V. Y. Merritt, and R. Srinivasan, Tetrahedron Lett., 4407 (1973).
14. C. Smith, J. Kalo, B. E. North, and D. Ginsburg, Tetrahedron, 30, 479 (1974).
15. P. Warner, R. LaRose, and T. Schleis, Tetrahedron Lett., 1409 (1974).
16. D. Ginsburg, Accounts Chem. Res., 2, 121 (1969).
17. Z. W. Bernstein, Massachusetts Institute of Technology Seminar in Organic Chemistry, February 25, 1969.
18. D. Ginsburg, Accounts Chem. Res., 5, 249 (1972).
19. E. Vogel, presented before the Robert A. Welch Foundation Conference on Chemical Research. XII. Organic Synthesis, Houston, Texas, Nov. 1968, p. 215.
20. G. D. Sargent, N. Lowry, and S. D. Reich, J. Amer. Chem. Soc., 89 5985 (1967).

21. G. L. Thompson, W. E. Heyd, and L. A. Paquette, J. Amer. Chem. Soc., 96, 3177 (1974).
22. M. S. Newman, Accounts Chem. Res., 5, 354 (1972).
23. P. Warner and S. L. Lu, J. Amer. Chem. Soc., 95, 5099 (1973).
24. P. V. R. Schleyer and G. W. Van Dine, J. Amer. Chem. Soc., 88, 2321 (1966), and references cited therein.
25. P. G. Gassman, E. A. Armour, J. Amer. Chem. Soc., 95, 6129 (1973)
26. P. G. Gassman, R. N. Steppel, and E. A. Armour, Tetrahedron Lett., 3287 (1973).
27. L. A. Paquette, R. E. Wingard, Jr., and J. M. Photis, J. Amer. Chem. Soc., 96, 5801 (1974).
28. N. J. Goldstein, J. Amer. Chem. Soc., 89, 6357 (1967); M. J. Goldstein and R. Hoffmann, ibid., 93, 6193 (1971).
29. L. A. Paquette and G. L. Thompson, J. Amer. Chem. Soc., 94, 7127 (1972).
30. W. B. Avila and R. A. Silva, Chem. Comm., 94 (1970).
31. M. Korat, D. Takarsky, and D. Ginsburg, Tetrahedron, 28, 2315 (1972).
32. K. Weinges and K. Klessing, Chem. Ber., 107, 1915 (1974).
33. G. Wittig and W. Schoch, Justus Liebigs Ann. Chem. 749, 38 (1971).
34. O. Schiacovelli, W. V. Philipsborn, C. Smith, and D. Ginsburg, Tetrahedron, 26, 4589 (1970).
35. D. Ginsburg, Accounts Chem. Res., 7, 286 (1974).
36. M. Korat, G. Schmuckler, and D. Ginsburg, J. Chem. Soc., 10A, 1784 (1970).
37. P. E. Eaton and G. H. Temme III, J. Amer. Chem. Soc., 95, 7508 (1973).
38. K. B. Wiberg, G. A. Epling, and M. Jason, J. Amer. Chem. Soc., 96, 912 (1974).
39. M. E. Jason, J. A. McGinnety, K. B. Wiberg, J. Amer. Chem. Soc., 96, 6531 (1974).

CROWN ETHERS: CONTROL OF ION STRUCTURE AND REACTIVITY

Reported by Maurice J. Baillargeon December 12, 1974

INTRODUCTION

The wide spread use of crown ethers began shortly after the first of what Cram[1] called the "Pedersen Papers."[2] A number of reviews have since dealt with the chemistry of crown ethers.[3] This seminar will deal with the nature of crown ether complexation plus the recent uses of crown ethers in organic chemistry with particular emphasis on the study of bimolecular eliminations and product control due to the presence of crown ethers.

The general structure of the crown ethers covered in this seminar is given in Figure 1. These macrocyclic polyethers can be assigned a unique name by application of the IUPAC rules for bridged hydrocarbons. For example, **1a** is called 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}] hexacosane.[2f] The common and much less cumbersome name of **1a** is dicyclohexyl-18-crown-6.

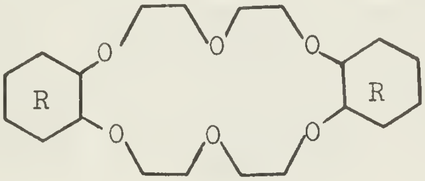


Figure 1

1a R=cyclohexyl: dicyclohexyl-18-crown-6
1b R=phenyl: dibenzo-18-crown-6

The ability of crown ethers to form complexes with salts and certain other compounds is perhaps the most remarkable property of these cyclic polyethers. This property has been the source of much experimental work; the presence of crown ethers has often altered the course or conditions of an organic reaction.[2f]

For example, in Pedersen's first articles[2a] the utilization of crown ethers in the saponification of the hindered esters of 2,4,6-trimethylbenzoic acid was illustrated. The methyl ester was hydrolyzed in heated toluene (105-111°) by a complex of potassium hydroxide with dicyclohexyl-18-crown-6 to the extent of 93% within 5 hours. Compared to this, no measurable saponification occurred when the methyl ester was refluxed for the same time at 75.5-77° with excess potassium hydroxide in 1-propanol. Pedersen suggested that the increased activity of the potassium hydroxide complex of dicyclohexyl-18-crown-6 was due to the presence of unsolvated hydroxyl ions which could attack the carbonyl group of the hindered ester much more readily than the ordinary solvated hydroxyl ions. Since this first work, more thorough and systematic studies of differing behavior of organic molecules with respect to complexed and uncomplexed species have been carried out.

EFFECT OF COMPLEXATION ON ION STRUCTURE

Fluorenyl salts are of particular importance in the study of contact versus solvent-separated ion pairs in solutions of alkali carbanion salts, since distinctly separated absorption maxima in the uv and visible spectra are observed for the two kinds of ion pairs.[4] Smid and Hogen Esch have reported their studies of the complexation of difluorenyl barium (Ba^{2+}, F_2^{2-}) with dimethyldibenzo-18-crown-6 in THF or pyridine. The barium carbanion salt showed a typical contact-ion-pair spectrum in THF, with an absorption maximum at 347 nm. When an equimolar quantity of dimethyldibenzo-18-crown-6 was added to Ba^{2+},F_2^{2-} in THF, the absorption spectrum revealed approximately equal fractions of contact and separated ion pairs, with maxima at 349 and 372 nm, respectively. The rate of exchange of barium-complexed crown ether with uncomplexed crown ether was measured using nmr. At 60° for 0.1M cyclic polyether (CPE) in pyridine, the rate constant for the reaction $Ba^{2+}, F_2^{-}\text{-CPE} + \text{CPE}^* \rightarrow Ba^{2+}, F_2^{2-}\text{-CPE}^* + \text{CPE}$

was approximately 500 $M^{-1}sec^{1}$.

In further studies of the binding of cyclic polyethers to ion-pairs of carbanion alkali salts,[5] variable temperature nmr along with optical spectral measurements showed that complexing of the crown ether with the ion-pairs of a fluorenylsodium salt led to strong upfield shifts in the nmr spectrum of the polyether ring protons. Exchange rates were determined at different temperatures which permitted the calculation of an activation energy of 12.5 kcal/mole for the reaction F^-, CPE, Na^+ + $CPE^* \rightarrow F^-$, CPE^*, Na^+ + CPE (CPE is dimethyldibenzo-18-crown-6). For comparison with the rate constant determined for the barium case, the calculated rate constants for the sodium case at -18° is 550 M^-sec^{-1}.

Competitive complexation in ion pair mixtures was a technique employed when ion-pair complexation constants were too high to measure spectrophotometrically, such as those of fluorenylsodium with dibenzo-18-crown-6.[6] The complexing preference of a crown ether for a particular cation may therefore be determined.

For example, when fluorenylsodium (λm=356nm) in THF was mixed with an equimolar quantity of the fluorenylpotassium-dimethyl-dibenzo-18-crown-6 (λm=373nm) complex, the crown ether favored complexation with the fluorenylsodium ion pair as seen by the appearance of the fluorenyl$^-$,K^+ contact ion pair maximum at 362 nm. The reaction that occurred was:

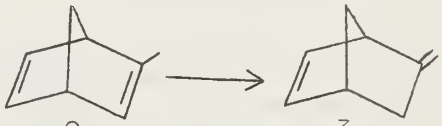
$$\underset{\lambda m=373nm}{\text{fluorenyl}^-,\ \text{CPE},\ \text{K}^+} + \underset{356nm}{\text{fluroenyl},\ \text{Na}^+} \longrightarrow$$

$$\underset{\lambda m=373nm}{\text{fluorenyl}^-,\ \text{CPE},\ \text{Na}^+} + \underset{362nm}{\text{fluorenyl}^-,\ \text{K}^+}$$

The order of selectivity of dimethyldibenzo-18-crown-6 using this technique was determined to be $Na^+ > K^+ > Cs^+ > Li^+$ in THF. When this experiment was carried out in oxetane, a solvent more basic than tetrahydrofuran, addition of fluorenyl CPE, K^+ to an oxetane solution of fluorenylsodium did not lead to a transfer of the polyether to the fluorenylsodium. Clearly then, the order of crown ether selectivity is solvent-dependent. It has been suggested that with oxetane as solvent, removal of the oxetane solvation shell by the crown ether from around the Na^+ ion was not energetically favored.

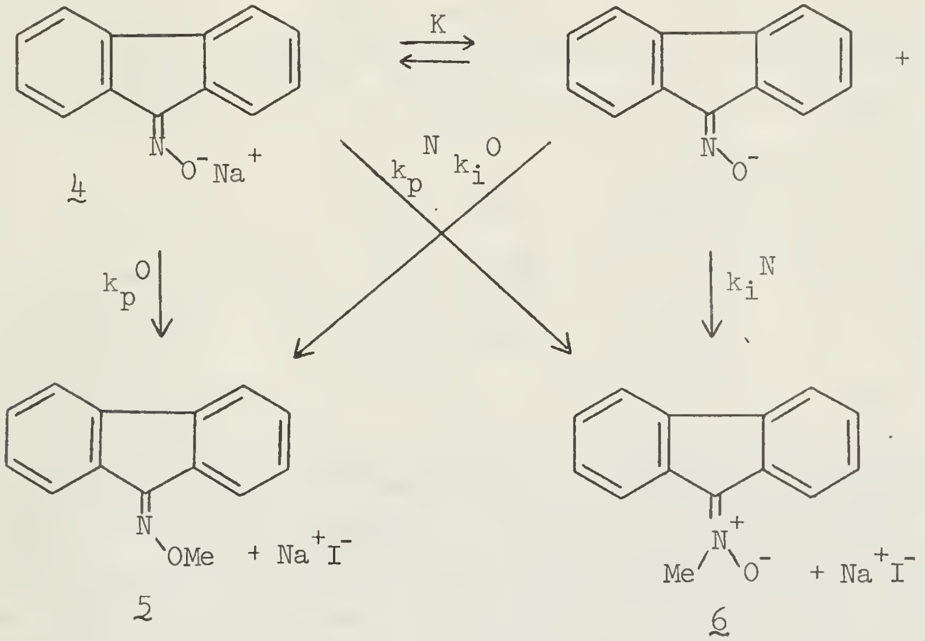
COUNTER ION REACTIVITY

As the selectivity order of crown ethers for cations has been determined to be solvent-dependent, so also has the reactivity of the counter ion been found to be influenced by solvent and the added presence of crown ether. Maskornick[7] measured the rate of the isomerization of 2-methylbicyclo[2.2.1]hepta-2,5-diene (2) to 5-methylenebicyclo[2.2.1]hepta-2-ene (3).


2 3

Isomerization was carried out in DMSO with potassium *t*-butoxide in the presence and absence of 18-crown-6. At *t*-butoxide base concentrations greater than 0.1 M, there was a zero order base dependence, while below this concentration the order varied until it reached first order at high dilution. When this experiment was repeated with a molar equivalent of 18-crown-6 added to complex the potassium ion, the kinetics followed first order dependence over the *t*-butox concentration range of 0.01M to 0.33 M. Maskornick felt that these experimenta observations could be attributed to the degree of base aggregation. At low concen trations in DMSO and in the presence of a polycyclic crown ether, the base was mostly monomeric; at higher concentrations, base aggregation increased in DMSO, but the crown ether effectively attracted K$^+$ and prevented the formation of aggregates.

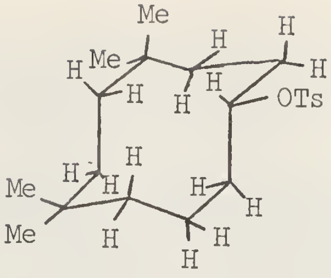
Related to this phenomenon of monomer versus aggregates as reacting species was Smith's study of the reaction of sodium 9-fluorenone oximate with methyl iodide in a solvent mixture of 33.5% acetonitrile and 66.5% tert-butyl alcohol.[8] In order to promote the dissociation of species 4, dibenzo-18-crown-6 was added to the reaction solvent. The visible absorption spectrum of 4 showed a shoulder at 424 nm; in the presence of dibenzo-18-crown-6 the shoulder shifted to a separate band with λ_{max} at 470 nm. This change was taken to indicate the conversion of a contact ion-pair into a separated ion-pair.[8a]



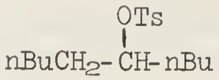
Reaction of 4 with methyl iodide gave a mixture of N- and O-alkylated products. The percent O-alkylated product formed depended upon oximate concentration, increasing from 47% at 88 x 10^{-3} M to a maximum value of 65% at < 1 x 10^{-3} M 4. In contrast, alkylation in the presence of dibenzo-18-crown-6 over an oximate concentration of about 4 to 50 x 10^{-3} M yielded the O-alkylated product in 61 to 66%. The addition of an excess of Na(C$_6$H$_5$)$_4$B was found to depress the rate of the alkylation reaction by a factor of 70. The high percentage of O-alkylation in the presence of a crown ether plus the high rate constants relative to those observed in the presence of the ion-pair dissociation suppressor Na(C$_6$H$_5$)$_4$B along with the visible spectrum shift were taken to indicate that the sodium salt was essentially dissociated in the presence of a crown ether. The work of both Smith and Maskornick illustrated the utility of crown ethers in effectively lessening the state of aggregation or increasing the degree of dissociation of a contact ion-pair in solution.

THE APPLICATION OF CROWN ETHERS TO ELUCIDATION OF THE MECHANISM OF ELIMINATION REACTIONS

Crown ethers were used to investigate the elimination reactions of 7 and 8. A number of deuterium-labeled derivatives of tosylate 7 have been synthesized[11] and used as model compounds in a mechanistic study of the elimination. Compounds 9, 10, and 12 were all found to undergo elimination without loss of deuterium. Compounds 11 and 13, however, suffered almost complete loss of the deuterium label. This indicated that the trans-β-hydrogen reacted predominately in the olefin formation.

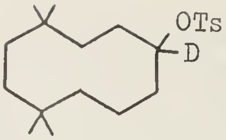


7

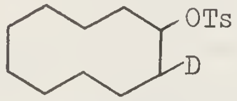


$$nBuCH_2\text{-}\overset{OTs}{CH}\text{-}nBu$$

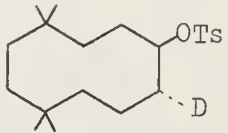
8



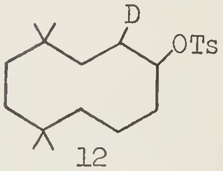
9



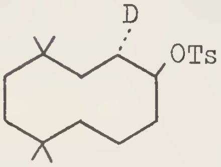
10



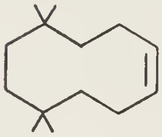
11



12

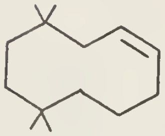


13



cis + trans

14



cis + trans

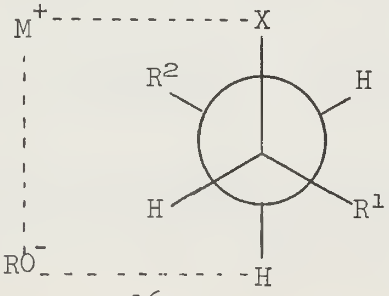
15

Examination of a model of 7 showed that the trans product could arise by syn-elimination and the cis product by anti-elimination. Thus, a change in reaction conditions which influenced the manner of elimination (syn versus anti) would be noted from changes in isomer distribution of elimination product.

Závada[9] used dicyclohexyl-18-crown-6 to study the nature of the potassium t-butoxide eliminations of compound 7. He determined that in benzene trans-olefin formation (syn elimination) was the overwhelming process. When an equimolar amount of dicyclohexyl-18-crown-6 was added to the benzene-alkoxide solution before the reaction, cis-olefin (anti-elimination) predominated. This change was attributed to the contact ion-pair separating ability of the crown ether; the separated ions of potassium t-butoxide were responsible for predominate anti-elimination, while the contact-ions were responsible for olefin production via syn-elimination.

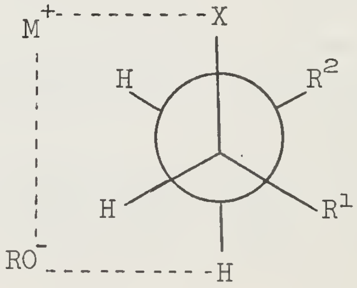
The acyclic compound 8 was also investigated.[10] Eliminations with potassium t-butoxide in benzene yielded cis- and trans-5-decene in a trans to cis ratio of .67; addition of dicyclohexyl-18-crown-6 caused a dramatic reversal in product composition with trans to cis ratio now 2.19.

Závada[10] stated without providing experimental proof, that eliminations of 8 in all solvents were due predominately to a trans pathway, and in a more recent publication[12] he proposed the following two transition states to explain his results. In the anti-pathway the approaching base interferes



16

anti-trans



17

anti-cis

with the alkyl portion; as interference will be considerably more severe in transition state 16 than in 17, the cis product should prevail.

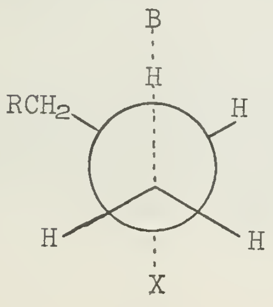
Similar results were found by Bartsch[13] in the 2-butyltosylate system: elimination with potassium t-butoxide in t-butanol gave predominantly cis-2-butene while a very dramatic reversal of the trans to cis ratio occurred when the reaction was carried out in the presence of dicyclohexyl-18-crown-6. More extensive studies were conducted on the elimination reactions of 2-bromobutane under the same conditions.[13] As the concentration of base increased, the relative proportion of 1-butene increased, and the trans- to cis ratio of 2-butenes decreased. Base association in solvents of low polarity was thought to influence the product distribution, as addition of crown ether was accompanied by marked changes in trans to cis product ratio. (cf Table 1)

Table 1. Factors Influencing Product Distribution in the Elimination Reactions of 2-Bromobutane[a]

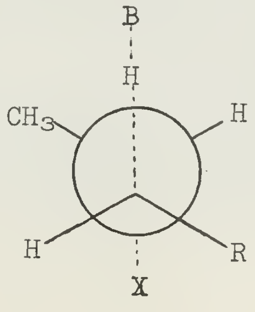
Base (conc)	Solvent	Product Distribution 2-Butenes trans/cis	1-Butene %
1. t-BuOK(0.50M)	t-BuOH	1.66	44.1
2. t-BuOK(0.50M) + dicyclohexyl-18-crown-6(0.28M)	t-BuOH	2.92	32.5
3. t-BuOK(0.50M)	DMSO	3.16	30.6
4. t-BuON-n-Pr$_4$(0.25M)	t-BuOH	2.99	31.3
5. Potassium 3-ethyl-3-pentoxide(0.25M)	3-ethyl-3-pentanol	1.04	63.1
6. Potassium 3-ethyl-3-pentoxide(0.25M) + dicyclohexyl-18-crown-6(0.25M)	3-ethyl-3-pentanol	2.82	37.3

[a] [2-Bromobutane] = 0.09-0.10 M

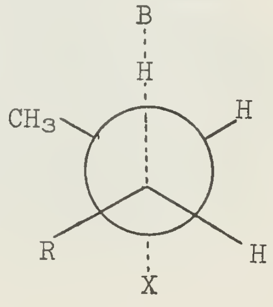
Bartsch proposed three transition states to account for the product ratios. If one assumes that the steric requirements of alkali metal-alkoxide ion pair aggregates are large, then the interaction of the associated base with the α- and β-alkyl groups should decrease in the order 18, 20, and 19. Transition state 20 is less affected than 19 because the bulky base can be located predominately on the side of the developing bond where only base-hydrogen interactions occur. Examination of Table 1 shows that for the bulky associated base, a large percentage of 1-butene is formed together with a low trans to cis ratio (entries # 1,5). For the dissociated base promoted by the presence



18



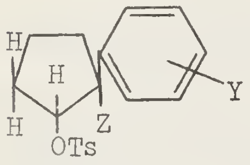
19



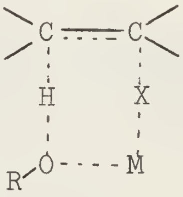
20

of crown ether a lower percentage of 1-butene is formed and a larger trans to cis ratio results (entries # 2,6).

An interesting example of the effect of base association upon competitive syn- and anti- elimination is seen with substituted *trans*-2-phenylcyclopentyl tosylate.[14,15] The relative ratio of 1-phenylcyclopentene (syn-elimination) to 3-phenylcyclopentene (anti-elimination) (9.8:1) which resulted from reaction of **21**a (0.025 M) with potassium *t*-butoxide (0.1M) in *t*-butanol was found to change dramatically when dicyclohexyl-18-crown-6 was present (0.43:1). A transition state in which the cation associates with the leaving group (**22**) has been proposed[9,10] to account for the effect of base association upon elimination in this case. A Hammett correlation for reactions of substituted derivatives of **21** indicated a ρ of +2.2 for reaction of **21** with associated base; with one equivalent of crown ether present ρ changed to +3.1. Also noted with the added presence of dicyclohexyl-18-crown-6 was the essentially constant value for k_H/k_D (5.1-5.3.) Bartsch indicated that the same k_H/k_D values for associated versus dissociated base showed that the relative transition-state force constants for O···H and H···C_β bonds were very similar. Thus, the more carbanionic transition states observed with the dissociated base as indicated by the larger ρ values apparently resulted from a dominant leaving group effect.



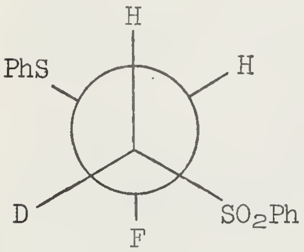
21a Z=H
Z=D



X=OTs, or Halide

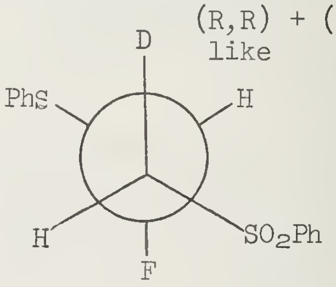
22

Paralleling these investigations of syn-elimination are studies of Naso on the syn-selectivity in reactions of phenoxide ion in dioxane with the diastereoisomeric 1-deuterio-2-fluoro-2-phenylthioethyl phenyl sulphones **23** and **24**.[16] Addition of dicyclohexyl-18-crown-6 caused the anti-pathway to increase in importance. Elimination of **23** and **24** induced by sodium *t*-butoxide in a mixed solvent (benzene-*t*-butanol (80:20)), however, was not influenced by the addition of crown ethers. This was taken to suggest that ion pairing and consequently base-leaving group interactions could not be considered the sole factor responsible for the syn-contribution.



(R,S) + (S,R) 'threo-like'

23



(R,R) + (S,S) 'erythr
like

24

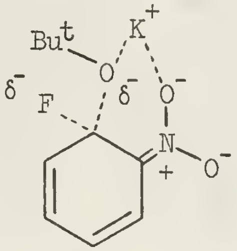
NAKED ANIONS AND CARBENES

Besides influencing the stereochemistry of elimination reactions, crown ethers have also been used to enhance the nucleophilicity of organic anions. Cyclic polyethers were used as additives in the study of potassium phenoxide nucleophilic reactivity as influenced by solvent. When examining the reaction of potassium phenoxide with 1-bromobutane, it was found that addition of 0.05 M of dicyclohexyl-18-crown-6 to a dioxane solution of 0.025 M potassium-phenoxide increased the alkylation rate of the phenoxide by a factor of 1.5×10^4.[17]

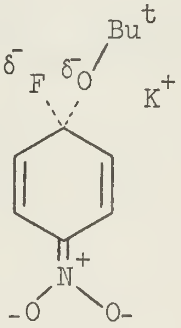
Differing cyclic ethers of the type dibenzo-3n-crown-n, where n was 4,5,6, and 8, were used to study the influence of the diameter of the cyclic ether cage on the rate of alkylation. The alkylation rate reached a maximum at n=6 while the rate dropped markedly for the polyether with n=8. This change in rate may be attributed to the necessity of matching the ring size to the cation to be complexed.

An increase in the rate of reaction of potassium *t*-butoxide in *t*-butanol with *ortho*- and *para*-fluoronitrobenzene has been examined in the presence and absence of crown ethers.[18] The k_o/k_p value for the reaction of potassium *t*-butoxide with the substituted nitro-fluorine derivatives was 3.6×10^2; upon addition of an equimolar amount of dicyclohexyl-18-crown-6 the k_o/k_p value shifted to 0.8.

The transition states **25** and **26** were used to rationalize this change. The potassium was thought to bridge the alkoxide and nitro-group oxygen atoms for the reaction with the ortho derivative **25**. Such an interaction is lacking in **26** which would account for its' lower reactivity. Addition of crown ether caused the reaction rate of 1-fluoro-4-nitrobenzene to increase by a factor of nearly 2000 while the rate of formation of *t*-butyl 2-nitrophenyl ether from **25** increased by only a factor of 3. Thus, the selective stabilization due to the potassium ion bridge was no longer important when crown ether was added to complex the potassium cation.



25

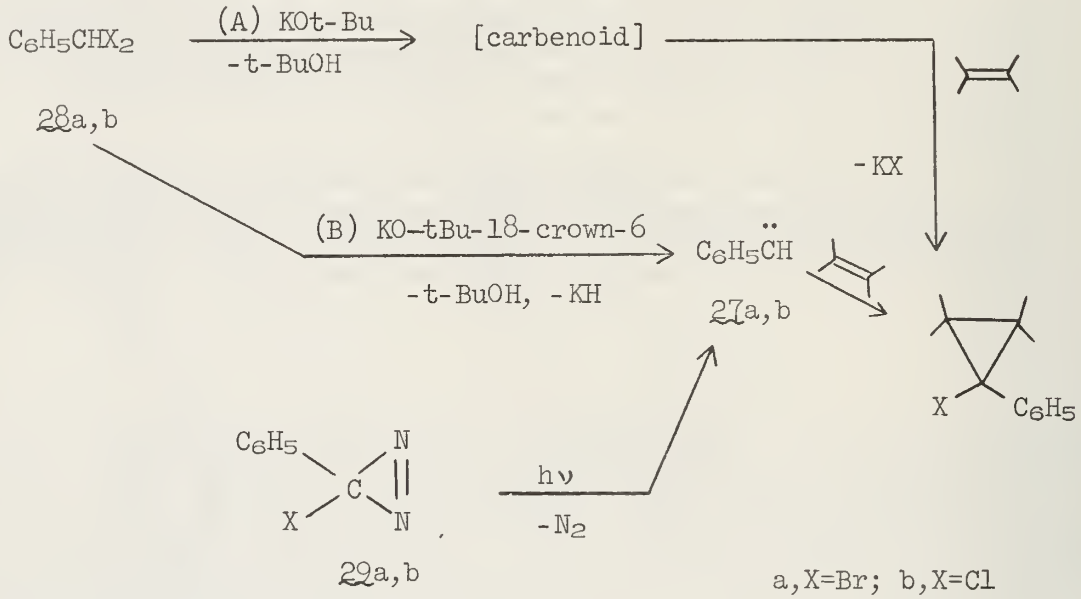


26

Liotta described his work with crown ethers and their influence on anion reactivity as the "chemistry of 'naked' anions".[19] The solubilization of potassium fluoride in acetonitrile and benzene using 18-crown-6 and reactions of the fluoride anion as both a base and a nucleophile have recently been investigated.[19] Displacement reactions at sp^3 hybridized carbon, competing elimination, plus displacement reactions at sp^2 hybridized carbon were illustrated. The reagent was prepared by dissolution of 18-crown-6 in dry acetonitrile or dry benzene followed by addition of dry potassium fluoride. Product yields were quantitative. For example, acetyl fluoride was prepared from acetyl chloride; also, one of the more mild and unusual reactions was the transformation of 2,4-dinitrochlorobenzene to 2,4-dinitrofluorobenzene. Potassium acetate showed the reactivity of a "naked" anion when complexed with 18-crown-6.[20] Benzyl acetate and n-hexyl acetate were synthesized from the corresponding bromides under mild conditions (25°) and in high yields (96-100%.)

The near quantitative synthesis of phenacyl esters from phenacyl bromide and potassium carboxylates could also be achieved.[21] Reactions run in benzene or acetonitrile with dicyclohexyl-18-crown-6 proceeded rapidly (10-30 min) under mild conditions (25-80°). In fact, even such sterically hindered acids as 2,4,6-trimethylbenzoic acid could be readily converted to phenacyl esters.

Moss and Pilkiewicz have generated free halocarbenes by utilizing crown ethers.[22] They were able to differentiate between the more selective carbenoid and the highly reactive free carbene 27, by observing the rates of competitive cyclopropanation of olefins with different degrees of substitution.



CONCLUSION

From the work presented in this seminar it is evident that crown ethers have found novel applications in the field of synthetic as well as physical organic chemistry by virtue of their unique complexing ability. The use of crown ethers as additives to organic reactions is limited solely by the chemist's imagination and will almost certainly continue to yield new and exciting results.

BIBLIOGRAPHY

1. E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, J. Amer. Chem. Soc., 95, 2691 (1973).
2. (a) C. J. Pedersen, J. Amer. Chem. Soc., 89, 2495, 7017 (1967); (b) C. J. Pedersen, Fed. Proc., Fed. Amer. Soc. Exp. Biol., 27, 1305 (1968); (c) C. J. Pedersen, J. Amer. Chem. Soc., 92, 386, 391 (1970); (d) C. J. Pedersen, J. Org. Chem., 36, 254, 1690 (1971); (e) M. R. Truter and C. J. Pedersen, Endeavour, 30, 142 (1971) and (f) C. J. Pedersen and H. K. Frensdorff, Angew. Chem., Int. Ed. Engl., 11, 16 (1972).
3. (a) C. Kappenstein, Bull. Soc. Chim. Fr. 89 (1974); (b) J. J. Christensen, J. O. Hill, R. M. Izatt, Science, 174, 459 (1971); (c) D. J. Cram and J. M. Cram, Science, 183, 803 (1974); (d) D. S. Mueller, University of Illinois Seminar, December 10, 1970; (e) F. Vögtle and P. Neumann, Chem. Zeit. 97, 600 (1973) and (f) J. J. Christensen, D. J. Eatough, and R. M. Izatt, Chem. Rev., 74, 351 (1974).
4. T. E. Hogen Esch and J. Smid, J. Amer. Chem. Soc., 91, 4580 (1969).
5. K. H. Wong, G. Konizer and J. Smid, J. Amer. Chem. Soc., 92, 666 (1970).
6. J. Smid, Angew. Chem. Internat. Edit., 11, 112 (1972).
7. M. J. Maskornick, Tetrahedron Lett., 1797 (1972).

8. (a) S. G. Smith and M. P. Hanson, J. Org. Chem., 36, 1931 (1971)
(b) S. G. Smith and D. V. Milligan, J. Amer. Chem. Soc., 90, 2393 (1968).
9. M. Svoboda, J. Hapala, J. Závada, Tetrahedron Lett., 265 (1972).
10. J. Závada, M. Svoboda, and M. Pánková, Tetrahedron Lett., 711 (1972).
11. M. Svoboda, J. Závada, and J. Sicher, Coll. Czech. Chem. Commun., 33, 1415 (1968)
12. J. Závada, M. Pánková, M. Svoboda and M. Schlosser, J. Chem. Soc., Chem. Comm., 168 (1973).
13. R. A. Bartsch, G. M. Pruss, D. M. Cook, R. L. Buswell, B. A. Bushaw, and K. E. Wiegers, J. Amer. Chem. Soc., 95, 6745 (1973).
14. R. A. Bartsch and K. E. Wiegers, Tetrahedron Lett., 36, 3819 (1972).
15. R. A. Bartsch, E. A. Mintz, and R. M. Parlman, J. Amer. Chem. Soc., 96 4249 (1974).
16. V. Fiandenese, G. Marchese, F. Naso and O. Sciacovell, J. Chem. Soc. P2, 1336 (1973).
17. L. M. Thomassen, T. Ellingsen and J. Ugelstad, Acta Chem. Scand., 25, 3024 (1971).
18. F. D. Cima, G. Biggi, and F. Pietra, J. Chem. Soc. P2, 55 (1973).
19. C. L. Liotta and H. P. Harris, J. Amer. Chem. Soc., 96, 2250 (1974).
20. C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, Tetrahedron Lett., 2417 (1974).
21. H. D. Durst, Tetrahedron Lett., 2421 (1974).
22. R. A. Moss and F. G. Pilkewicz, J. Amer. Chem. Soc., 96, 5632 (1974).

UNIVERSITY OF ILLINOIS-URBANA
Q.547IL6S C001
ORGANIC SEMINAR ABSTRACTS URBANA
1973/74-1974/75:1
3 0112 025513794